Synthesis of 2-Substituted Pyrimidines via Cross-Coupling Reaction of Pyrimidin-2-yl Sulfonates with Nucleophiles in Polyethylene Glycol 400

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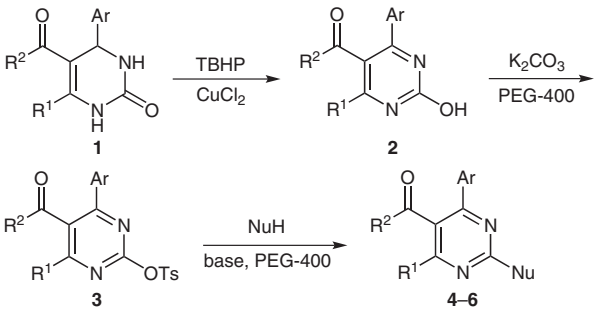
Abstract: A mild and rapid procedure to the synthesis of 2-substituted pyrimidines was developed via sequential functionalization of easily available Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones via oxidation, esterification, followed by cross-coupling reaction of pyrimidin-2-yl sulfonates with N, S, and O nucleophiles in PEG-400 as a green reaction medium at room temperature.

Keywords: 2-substituted pyrimidines, oxidation, esterification, cross-coupling reaction, PEG-400

Reducing or eliminating the use of volatile organic solvents can minimize waste formation, which is one of the key objectives in green chemistry. Recently, polyethylene glycol (PEG) and its monomethyl ethers have emerged as alternative green reaction medium with unique properties such as thermal stability, commercial availability, nonvolatility, immiscibility with a number of organic solvents, and recyclability. On the other hand, PEG is inexpensive, nonhalogenated, easily degradable, and possess low toxicity.[1] The use of PEG as a reaction solvent has received considerable attention in synthetic organic chemistry.[2]

Over the years, research interest in Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPM)[3] has surged rapidly owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core, such as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and hepatitis B virus replication inhibitors.[4] Several marine-derived natural products such as Crambine, Batzelladine B (potent HIV gp-120CD4 inhibitors), and Ptilomycalin alkaloids also contain the DHPM core.[5] Although pyrimidine derivatives are found in a wide range of biologically active molecules,[6] there has been a lack of a methodology to efficiently synthesize 2-substituted pyrimidines. In general, 2-substituted pyrimidines were obtained from Biginelli DHPM by a C-2 O/S substitution strategy involving aromatization, chlorination,[7] or sulfide oxidation[8] and coupling with a nucleophile. Aromatization of the Biginelli DHPM is known to be exceedingly difficult.[9] To our delight, Yamamoto et al.[10] developed a mild and practical procedure for dehydrogenation of DHPM using *tert*-butylhydroperoxide (TBHP) in 2005, and demonstrated on a large scale. Chlorination using $POCl_3$ at high temperatures could be problematic for substrates with sensitive functionalities,[7a] and S-alkylation was absolutely necessarily for sulfide oxidation.[8b,e] Organic solvents were widely used in the process. In 2005, Kang et al.[11] have described a two-step procedure to convert Biginelli DHPM to the C2-functionalized pyrimidines via Kappe dehydrogenation and PyBroP-mediated coupling with nucleophiles at room temperature for 24 hours. However, the synthesis of C2-functionalized pyrimidines has been predominantly carried out in organic solvents. Some limitations such as elevating temperatures, catalyst, and hazardous organic solvents were involved. Thus, the development of a simple and efficient method under green reaction conditions for constructing these compounds has been advocated.

Herein, we report a mild and rapid procedure for the synthesis of C2-substituted pyrimidines by sequential functionalization of easily available Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones via oxidation, esterification, followed by cross-coupling reaction of pyrimidin-2-yl sulfonates with N, S, and O nucleophiles in PEG-400 at room temperature (Scheme 1).



Scheme 1

The Biginelli DHPM **1** and their dehydrogenated compounds **2** were readily prepared according to the procedures by Matsushima et al.[12] and Yamamoto et al.[10] We noticed that sulfonic esters are important intermediates in organic synthesis.[13] The esterification reactions were carried out most frequently in dry dichloromethane or chloroform in the presence of triethylamine, pyridine, or aqueous sodium hydroxides as bases.[14] In this study, the pyrimidin-2-yl sulfonates **3** were prepared by employing

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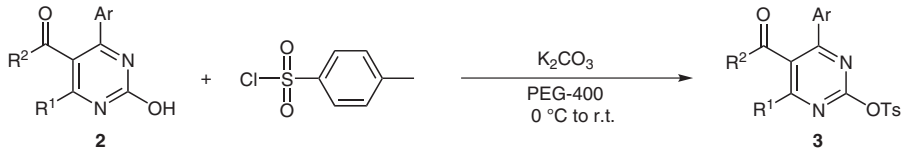
Table 1 Preparations of Pyrimidin-2-yl Sulfonates[a]



Entry	Ar	R^1	R^2	Product **3**	Yield (%)[b]
1	Ph	Me	OEt	**3a**	80
2	4-$MeOC_6H_4$	Me	OEt	**3b**	81
3	4-MeC_6H_4	Me	OEt	**3c**	79
4	4-ClC_6H_4	Me	OEt	**3d**	80
5	4-BrC_6H_4	Me	OEt	**3e**	82
6	4-FC_6H_4	Me	OEt	**3f**	85
7	4-FC_6H_4	*i*-Pr	OMe	**3g**	86
8[c]	Ph	Me	OEt	**3h**	83

[a] *Reaction conditions*: **2** (1.0 mmol), *p*-toluenesulfonyl chloride (1.5 mmol), K_2CO_3 (1.5 mmol), PEG-400 (2.0 g), 0 °C to r.t., ca. 40 min.
[b] Isolated yield.
[c] Benzenesulfonyl chloride (1.5 mmol).

PEG-400/K_2CO_3 system. To a suspension of compounds **2** (1 equiv) and *p*-toluenesulfonyl chloride (1.5 equiv) in PEG-400, K_2CO_3 (1.5 equiv) was added at 0 °C. The reaction mixture was stirred for 40 minutes at room temperature. After completion of the reaction, the mixture was poured into water and filtered, then recrystallized from ethanol to give the pure pyrimidin-2-yl sulfonates **3** in good to excellent yields (Table 1).[15]

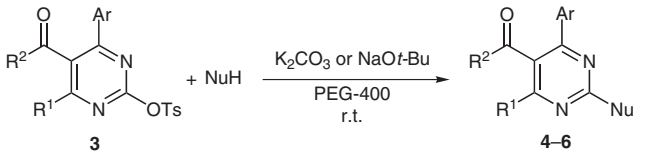
We began our coupling investigation with amines (Table 2).[16] Sulfonates **3a**–**g** were dissolved in PEG-400 and added to a mixture of amines (1.5 equiv) and K_2CO_3 (1.5 equiv) at room temperature. After stirring for 30–60 minutes, the reaction mixture was poured into water to induce precipitation. The solid was filtered and washed with copious amounts of water, then recrystallized from ethanol and petroleum ether to give the desired 2-aminopyrimidines **4a**–**p**. Over the course of this study, it was found that cyclic secondary amines were the most effective substrates for this process (entries 1–14). The nature of substituents on the heterocyclic fragment of sulfonate esters did not play a significant role in this reaction. Acyclic amines also gave promising results (completed within 60 min), but took a longer reaction time than that with secondary acyclic amines (entries 15 and 16). However, aromatic amines failed to react even under high temperature and long time (entry 17). Control experiments suggested that prolonged reaction times did not improve the product yields.

We next turned our attention to sulfur and oxygen nucleophiles (entries 18–24) by treating sulfonates **3** with 1.5 equivalents of S, O nucleophiles in PEG-400/K_2CO_3 or NaO*t*-Bu at room temperature. *p*-Thiocresol gave the corresponding 2-arylthiopyrimidines in 30 minutes (entries 18–20). However, $HOOCCH_2SH$ failed to react (entry 21). In addition, alcohols gave corresponding 2-alkyloxypyrimidines in 90 minutes (entries 22–24), while phenols provided O–S cleavage products under strongly basic NaO*t*-Bu (Table 3).[17] Hence after the reaction, phenolic toluenesulfonates **7** and compounds **2** were isolated.

It is noteworthy that the study reported above is the first exploration of cross-coupling reaction of pyrimidin-2-yl sulfonates with N, S, and O nucleophiles to give C2-substituted pyrimidines using PEG-400 as a green reaction medium at room temperature. This cross-coupling reaction was fast as compared to the other reported metal-catalyzed processes. In this study, we have also observed two competing pathways (i.e., C–O bond cleavage path vs. the S–O bond-cleavage path). Generally, the C–O bond-cleavage reaction is favored with stronger nucleophiles with a higher polarizability (amines, thiophenoxide). However, the S–O bond cleavage reaction is favored with those nucleophiles with a lower polarizability ($C_6H_5O^-$). Reaction of **3a** with $CH_3CH_2O^-$, $(CH_3)_2CHO^-$, $PhCH_2O^-$ produced C2-substituted pyrimidines via cleavage of C–O bond in high yields.

In conclusion, a simple, rapid, and environmentally benign methodology towards the synthesis of C2-substituted pyrimidines has been reported. A series of pyrimidin-2-yl sulfonates are excellent precursors for the generation of C2-substituted pyrimidines via cross-coupling of the reactive sulfonate group with different nitrogen, sulfur, and oxygen nucleophiles. Compared to other processes for the synthesis of C2-substituted pyrimidines and the cross-coupling of aryl sulfonates with nucleophiles, our protocol has the advantages of milder reaction conditions, faster reaction rate, and the use of nonmetal catalyst. Additionally, our protocol is a practical approach that uses

Table 2 Coupling of Pyrimidin-2-yl Sulfonates **3** with NuH



Entry	Sulfonate **3**[15]	NuH	Product[16,17]	Yield (%)[a]
1	**3a**	morpholine	**4a**	84[b]
2	**3b**	morpholine	**4b**	81
3	**3c**	morpholine	**4c**	83
4	**3d**	morpholine	**4d**	81
5	**3e**	morpholine	**4e**	85
6	**3f**	morpholine	**4f**	86
7	**3g**	morpholine	**4g**	80
8	**3a**	piperidine	**4h**	82
9	**3b**	piperidine	**4i**	80
10	**3c**	piperidine	**4j**	80
11	**3d**	piperidine	**4k**	83
12	**3e**	piperidine	**4l**	80
13	**3f**	piperidine	**4m**	82
14	**3g**	piperidine	**4n**	84
15[c]	**3a**	$EtNH_2$	**4o**	82
16[c]	**3a**	$HOCH_2CH_2NH_2$	**4p**	80
17	**3a**	4-$MeC_6H_4NH_2$		n.r.[d]
18	**3a**	4-MeC_6H_4SH	**5a**	80
19	**3b**	4-MeC_6H_4SH	**5b**	78
20	**3d**	4-MeC_6H_4SH	**5c**	81
21	**3a**	$HOOCCH_2SH$		n.r.[d]
22	**3a**	EtOH	**6a**	82[e]
23	**3a**	*i*-PrOH	**6b**	86
24	**3a**	BnOH	**6c**	80

[a] Isolated yield.
[b] Reaction conditions for compounds **4** and **5**: **3** (1.0 mmol), amine (1.5 mmol), K_2CO_3 (1.5 mmol), PEG-400 (2.0 g), r.t., 30 min.
[c] Completed within 60 min.
[d] No reaction.
[e] Reaction conditions for compounds **6a–c**: **3** (1.0 mmol), NuH (1.5 mmol), NaOt-Bu (1.5 mmol), PEG-400 (2.0 g), r.t., 90 min.

PEG-400 as a readily commercially available green solvent with low cost and recyclable property.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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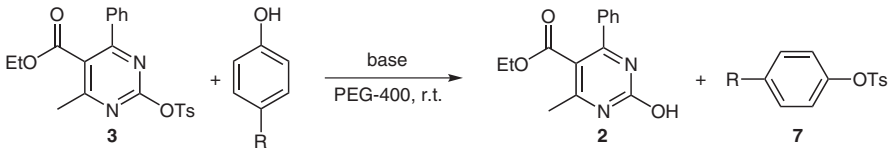
Table 3 Coupling of Pyrimidin-2-yl Sulfonates **3** with Phenol



Entry	Sulfonate **3**	R	Product **7**	Yield (%)[c]
1[a]	**3a**	H	**7a**	88
2[b]	**3a**	H	**7a**	90
3[a]	**3a**	Cl	**7b**	80

[a] Reaction conditions A: **3** (1.0 mmol), phenol (1.5 mmol), K_2CO_3 (1.5 mmol), PEG-400 (2.0 g), r.t., 60 min.
[b] Reaction conditions B: **3** (1.0 mmol), phenol (1.5 mmol), NaO*t*-Bu (1.5 mmol), PEG-400 (2 g), r.t., 90 min.
[c] Isolated yield.

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(15) **General Procedure for the Preparation of 3**
To a stirred mixture of compound **2** (1 mmol) and *p*-toluenesulfonyl chloride (1.5 mmol) in PEG-400 (2 g), K_2CO_3 (1.5 mmol) was added at 0 °C. The reaction mixture was taken slowly to r.t. and stirred for ca. 40 min. After complete conversion (TLC monitoring), the crude reaction mixture was poured into H_2O to induce precipitation. The solid was filtered and washed with copious amounts H_2O, then recrystallized from EtOH to give pure pyrimidin-2-yl sulfonates **3** as white solid.
Selected Data for Compound 3a
Mp 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, 3 H, *J* = 7.2 Hz), 2.45 (s, 3 H), 2.57 (s, 3 H) 4.20 (q, 2 H, *J* = 7.2 Hz), 7.32–8.03 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 21.7, 22.5, 62.2, 123.8, 128.5, 128.5, 129.3, 129.4, 130.8, 133.8, 136.3, 145.5, 158.7, 166.7, 167.2, 169.6. ESI-MS: *m/z* = 413 [M + H$^+$].
(16) **General Procedure for the Preparation of 4 and 5**
To a stirred mixture of compound **3** (1 mmol) in PEG-400 (2 g) at r.t. were added nucleophiles (1.5 mmol) and K_2CO_3 (1.5 mmol). After the mixture was stirred at r.t. for 0.5–1 h (TLC monitoring), it was poured into H_2O to induce precipitation. The solid was filtered and washed with copious amounts water, then recrystallized from EtOH and PE to give pure products **4** and **5** as white solid.
Selected Data for Compounds 4a
Mp 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, *J* = 7.2 Hz), 2.50 (s, 3 H), 3.76 (t, 4, *J* = 4.8 Hz), 3.93 (m, 3 H), 4.04 (q, 2 H, *J* = 7.2 Hz), 7.40–7.58 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 23.1, 44.1, 60.9, 66.9, 114.5, 128.1, 128.2, 129.5, 139.3, 160.2, 165.7, 167.0, 168.9. ESI-MS: m/z 328 ([M+H$^+$]).
Selected Data for Compounds 5a
Mp 65–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, 3 H, *J* = 7.2 Hz), 2.39 (s, 3 H), 2.50 (s, 3 H), 4.14 (q, 2 H, *J* = 7.2 Hz), 7.21–7.53 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 21.3, 22.6, 61.7, 121.4, 125.9, 128.3, 128.4, 129.7, 130.1, 135.1, 137.4, 139.2, 163.5, 165.8, 168.1, 172.4. ESI-MS: *m/z* = 365 [M + H$^+$].
(17) **General Procedure for the Preparation of 6**
To a stirred mixture of compound **3** (1 mmol) in PEG-400 (2 g) at r.t. were added nucleophiles (1.5 mmol) and NaO*t*-Bu (1.5 mmol). After the mixture was stirred at r.t. for 1.5 h (TLC monitoring), the reaction mixture was treated with H_2O, and extracted with EtOAc, the organiclayers were dried over Na_2SO_4. The crude product was purified by flash chromatography (PE–EtOAc, 10:1) to give pure products **6** as colorless oil.
Selected Data for Compound 6a
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.2 Hz), 1.34 (t, 3 H, *J* = 6.8 Hz), 2.47 (s, 3 H), 4.05 (m, 2 H), 4.40 (q, 2 H, *J* = 7.2 Hz), 7.30–7.56 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 14.2, 22.5, 61.3, 63.5, 119.5, 128.0, 128.1, 129.8, 137.7, 163.9, 166.2, 168.1, 168.4. ESI-MS: *m/z* = 287 [M + H$^+$].