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Direct metal-free *O*-arylation of Biginelli 4-aryl-6-methyl-pyrimidine-2(1*H*)-one derivatives using diaryliodonium salts

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ABSTRACT

4-Aryl-6-methyl-pyrimidine-2(1*H*)-one scaffolds of Biginelli type were subjected to C–O cross-coupling reactions using symmetrical diaryliodonium salts under transition metal-free conditions to afford 2-aryloxy pyrimidine derivatives in good to excellent yields.

In the last two decades, Biginelli 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) scaffolds have received considerable attention due to a wide range of pharmaceutical properties such as antibacterial, antitumor, anti-inflammatory, calcium channel blockers, antihypertensive agents, α_{1a}-antagonists, and neuropeptide Y (NPY) antagonists.[1] In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also showed interesting biological properties.[2] Owing to these pharmacological properties, there is a growing interest to make post-modification of DHPM scaffolds furnish 'drug like' small molecules for biological screening.[3] For example, the C2 position of DHPMs has been modified by the introduction of a wide range of N, O, and C-nucleophiles to form 2-substituted pyrimidine derivatives.[4] The pyrimidin-2(1*H*)-one derivative, obtained by the oxidative dehydrogenation of DHPMs, is generally a necessary intermediate for the introduction of nucleophilic species at 2-position.[5] In particular, the introduction of oxygen nucleophile at 2-position of Biginelli DHPMs furnishes 2-aryloxy pyrimidine derivatives. Apart from Biginelli pyrimidin-2(1*H*)-one derivatives, other cyclic amides such as quinazolin-4(3*H*)-one[6] and pyridin-2(1*H*)-one[7] have also received a considerable attention for the *O*-arylation at 2-position to form heteroaryl ethers which are also found to be the sub-structural unit of various pharmaceuticals, herbicides, and functional materials (Fig. 1).[8]

The synthesis of heteroaryl ethers of these cyclic amides is generally achieved through activation at 2-position of pyrimidin-2(1*H*)-ones using TsCl, Ac_2O, and $POCl_3$ followed by aromatic nucleophilic substitution (S_NAr) with electron deficient phenolic compounds (Scheme 1).[9] However, this two-step strategy results in low yields of 2-heteroaryl ether and requires harsh condition during chlorination using $POCl_3$ at high temperatures. Some of the drawbacks of S_NAr process for 2-heteroaryl ether synthesis have been overcome by the oxidative Pd-catalyzed C–O cross-coupling reaction of pyridotriazol-l-yloxypyrimidines with arylboronic acids in the presence of dioxygen.[10] Recently, the Mitsunobu reaction of 2-hydroxy pyrimidine with phenols using DIAD and PPh_3 has been demonstrated for the synthesis of 2-aryloxy pyrimidine.

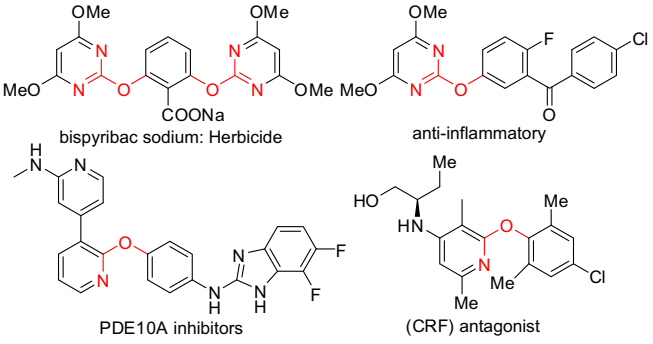

Figure 1. Examples of biologically active molecules that have heteroaryl ether core structure

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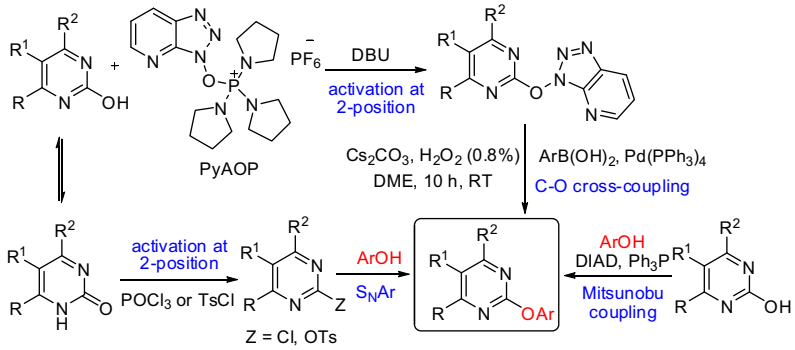
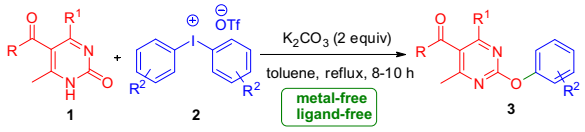


Scheme 1. Literature methods of 2-aryloxy pyrimidine synthesis.



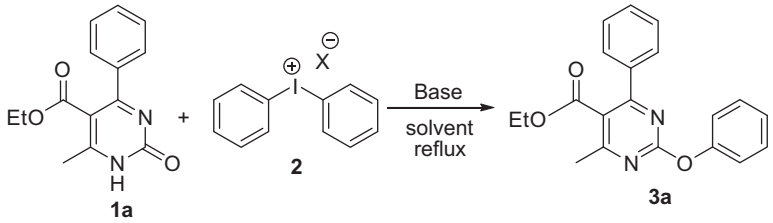
Scheme 2. *O*-Arylation of 4-aryl-6-methyl-pyrimidine-2(1*H*)-one derivatives using diaryliodonium salts.

However, this strategy is mainly successful with phenols bearing electron withdrawing groups.[11]

Diaryliodonium salts are an important class of hypervalent iodine compounds.[12] They have received renewed interest in organic synthesis as more reactive version of iodoarenes for various C–C, C–O, C–N, and C–S cross-coupling reactions. They have emerged as a source of aryl cation in the *O*-arylation of phenols,[13] carboxylic acids,[14] alcohols,[15] vicinal diols,[16] and *N*-hydroxyphthalimide.[17] The cyclic amides are in tautomerism with 2-hydroxy pyrimidine or pyridine and therefore, we were intrigued with the possibility of C–O cross-coupling reaction with diaryliodonium salts. Herein, we report the direct C–O cross-coupling reactions of 4-aryl-6-methyl-pyrimidine-2(1*H*)-one derivatives using symmetrical diaryliodonium salts to afford 2-aryloxy pyrimidine derivatives under metal-free conditions (Scheme 2).

The requisite 4-aryl-6-methyl-pyrimidine-2(1*H*)-ones **1** were obtained by the oxidative dehydrogenation of Biginelli 3,4-dihydropyrimidone using the literature methods.[19] Similarly, the symmetrical diaryliodonium salts **2** (R^2 = H, Br, Cl, and CH_3) were prepared using the Olofsson method.[20] The *O*-arylation of 4-phenyl-6-methyl-pyrimidine-2(1*H*)-one **1a** using diphenyliodonium salts was chosen as a model reaction (Table 1). Among the solvents tested, acetonitrile and toluene gave satisfactory yields of *O*-arylation products while DMF, THF, and 1,4-dioxane were found to be inferior (entries 1–5). The *O*-arylation reaction did not proceed in the absence of base (entry 6). Other bases such as NaOH and Et_3N were found to be less efficient compared to K_2CO_3 (entries 7 and 8). The *O*-arylation of **1a** using diphenyliodonium tetrafluoroborates and chlorides was not significant compared to diphenyliodonium triflates (entries 9 and 10). Thus, the combination of diphenyliodonium triflate with K_2CO_3 as the base in toluene was found to be the most suitable for *O*-arylation of **1a**. Therefore, we gradually changed the quantity of **2** and K_2CO_3 in subsequent optimization studies which revealed that the formation of **3a** took place in all the cases (entries 11–14). However, the maximum yield

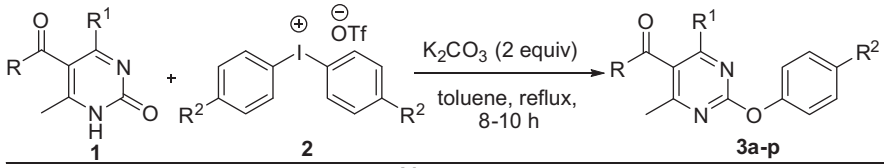
Table 1
Optimization of *O*-arylation of Biginelli ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate **1a**

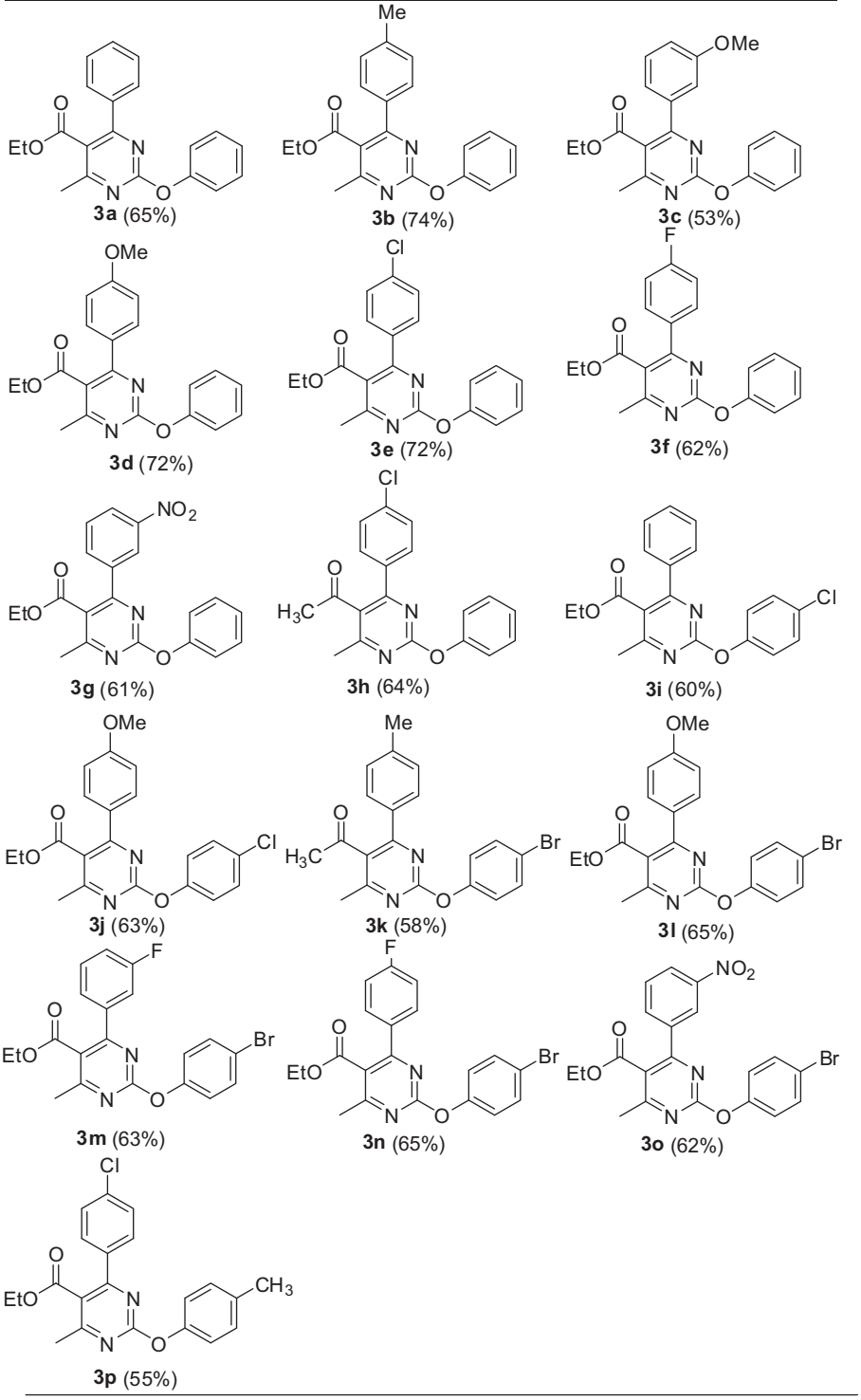


Entry	Ph_2IOX	Base	Solvent	Time (h)	Yield of **3a** (%)[a]
1	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.0 equiv)	DMF	24	12
2	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.0 equiv)	THF	24	17
3	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.0 equiv)	Dioxane	24	23
4	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.0 equiv)	CH_3CN	24	39
5	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.0 equiv)	Toluene	24	43
6	Ph_2IOTf (1.0 equiv)	—	Toluene	24	0
7	Ph_2IOTf (1.5 equiv)	NaOH (2.0 equiv)	Toluene	24	14
8	Ph_2IOTf (1.5 equiv)	Et_3N (2.0 equiv)	Toluene	24	49
9	Ph_2IBF_4 (1.5 equiv)	K_2CO_3 (2.0 equiv)	Toluene	24	46
10	Ph_2ICl (1.5 equiv)	K_2CO_3 (2.0 equiv)	Toluene	24	52
11	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.2 equiv)	Toluene	24	49
12	Ph_2IOTf (1.0 equiv)	K_2CO_3 (1.5 equiv)	Toluene	24	52
13	Ph_2IOTf (1.2 equiv)	K_2CO_3 (1.5 equiv)	Toluene	15	60
14	**Ph_2IOTf (1.5 equiv)**	**K_2CO_3 (2.0 equiv)**	**Toluene**	**10**	**65**

[a] Isolated yields.

Table 2
Synthesis of 2-aryloxy pyrimidine derivatives using diaryliodonium triflates[a]





[a] Reaction conditions: 4-aryl-6-methyl-pyrimidine-2(1*H*)-one derivatives (2 mmol), diaryliodonium triflate (3 mmol), and K_2CO_3 (4 mmol) in 10 mL toluene under reflux for 8–10 h.

of **3a** (65%) was achieved using 1.5 and 2.0 equiv of diphenyliodonium triflate and K_2CO_3, respectively.[18]

Under these optimized conditions, the reactions of various 4-aryl-6-methyl-pyrimidine-2(1*H*)-one derivatives with four different symmetrical diaryliodonium triflates **2** (R^2 = H, CH_3, Br, and Cl) were performed (Table 2). In general, good to excellent yields of *O*-arylation products were obtained in all the cases. The electron-withdrawing and donating groups present on 4-aryl substituent were tolerated under the reaction conditions. All the products were characterized by IR, NMR (^{1}H and ^{13}C), and LCMS analysis (Supplementary data).

In summary, we have developed a new method for the *O*-arylation of 4-aryl-6-methyl-1,2-dihydropyrimidines using diaryliodonium salts under transition metal-free conditions. A wide range of 2-aryloxy pyrimidine derivatives were obtained in good to excellent yields. Compared with previous procedures, this method is a direct strategy for the synthesis of 2-aryloxy pyrimidines and avoids the activation at 2-position (chlorides, tosylates, and pyridotriazol-1-yloxy) of 1,2-dihydropyrimidines.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR spectra, and LCMS are provided for all the compounds synthesized) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.079.

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