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Synthesis and Suzuki–Miyaura reactions of 5-halo-3,4-dihydropyrimidin-2(1*H*)-ones

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ABSTRACT

A novel synthesis of 6-methyl-4-phenyl-5-substituted-3,4-dihydropyrimidin-2(1*H*)-ones from 6-methyl-4-phenyl-5-halo-3,4-dihydropyrimidin-2(1*H*)-ones via the Suzuki–Miyaura reaction is reported. These previously unknown heterocyclic halides are easily prepared using the Biginelli multicomponent reaction followed by halodecarboxylation. The effect of varied substitution at the C-4 position on the cross-coupling reaction is also examined.

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) exhibit a spectrum of interesting pharmacological properties.[1] The synthesis of these privileged structures has therefore received considerable attention. Many improved variations of the original Biginelli multicomponent reaction have been developed in recent years.[2–4] A number of methods for facile elaboration of DHPM scaffolds have also been recently reported.[5–8]

The Biginelli multicomponent condensation is quite general in that a wide variety of aldehydes, ureas, and thioureas can participate. A variety of active methylene compounds can also be utilized enabling diversity at the C-5 and C-6 positions (Fig. 1).[9] However, the availability of active methylene substrates and their potentially variable ability to take part in the multicomponent condensation might limit the application of this approach. Considering this, it was envisioned that the synthesis of a halogenated intermediate could facilitate the generation of C-5-substituted analogs via cross-coupling reactions (Fig. 2). Significantly, this would allow access to C-5 substitutions which might not be directly obtainable from the Biginelli condensation.

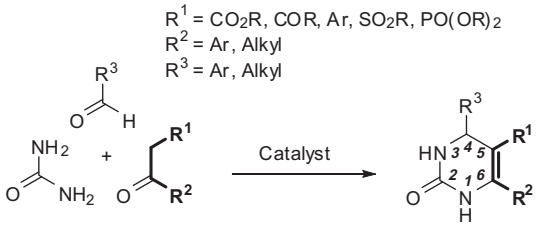


Figure 1. The Biginelli reaction

Previous investigations have demonstrated that some 5-carboxylic acid DHPMs readily decarboxylate at reflux in aqueous methanolic sodium hydroxide.[10] It was therefore speculated that the application of Hunsdiecker-type chemistry could generate the desired synthetically useful and previously unknown 5-halo DHPMs (Fig. 2).

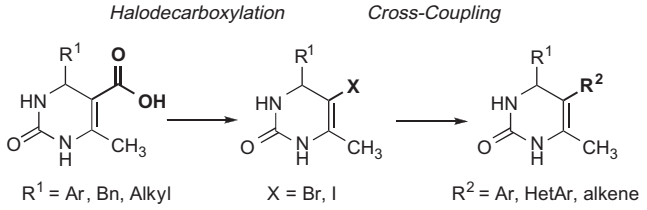
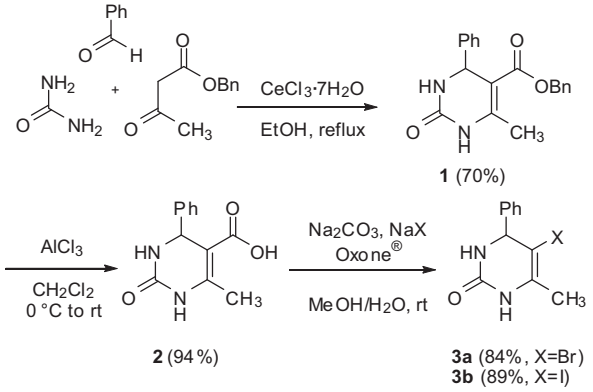


Figure 2. General scheme for synthesis and application of C-5 halogenated DHPMs.



Scheme 1.

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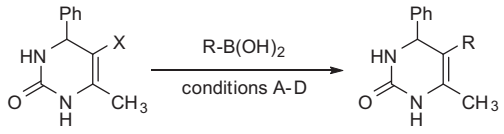
A 5-carboxylic acid DHPM **2** was synthesized in two steps (Scheme 1). The benzyl ester **1** was generated utilizing a cerium(III) chloride-catalyzed protocol that provided a yield comparable to recent literature examples.[11] An analogous methyl ester was originally synthesized but was difficult to hydrolyze to the carboxylic acid despite a report to the contrary.[10] The resistance of 5-carboxylic acid esters of DHPMs to hydrolysis has been noted in some instances.[12] Deprotection of **1** to the carboxylic acid **2** was accomplished in an excellent yield using aluminum trichloride.

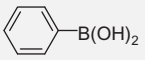
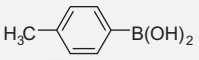
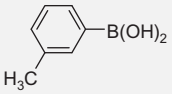
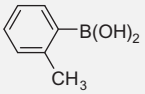
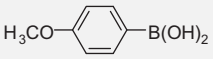
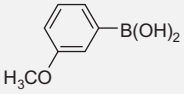
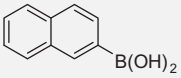
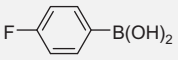
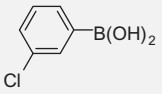
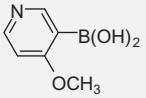
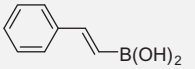
Hydrogenation with palladium on carbon in ethanol at room temperature or treatment with iodotrimethylsilane in chloroform at 60 °C could also be used for debenzylation of **1**. However, aluminum trichloride provided superior yields and greater operational simplicity upon scale-up.[13] Treatment of **2** with Oxone® and a sodium halide in basic aqueous methanol followed by filtration gave good yields of bromide **3a** or iodide **3b**.[14] Other decarboxylative halogenation conditions including NBS with a variety of bases, pyridinium bromide perbromide, and tetrabutylammonium bromide/Dess–Martin reagent gave inferior results.[15–17] Attempts to synthesize 5-halo DHPMs directly from a multicomponent condensation of benzaldehyde, urea, and haloacetones gave only traces of the desired products.

Table 1
Suzuki–Miyaura reactions of 5-halo-DHPMs



3a (X = Br)
3b (X = I)

4 (0-92%)

Entry	R-B(OH)$_2$	Halide, coupling protocol	Isolated yield (%), **4**
1		**3a**, A	92
2		**3b**, A	90
3		**3b**, C	67
4		**3b**, D	n.d.[a]
5		**3a**, A	72
6		**3a**, A	90
7		**3a**, A	>10[b]
8		**3a**, B	>10[b]
9		**3a**, A	86
10		**3a**, A	78
11		**3a**, A	91
12		**3a**, A	>5[b]
13		**3a**, B	>5[b]
14		**3a**, C	58
15		**3b**, C	53
16		**3a**, C	27
17		**3a**, C	45
18		**3a**, C	40

Reaction conditions: (A) 2.0 equiv RB(OH)$_2$, 5.0 equiv KF, 0.05 equiv Pd$_2$(dba)$_3$, 0.05 equiv Pd(*t*Bu$_3$P)$_2$, tetrahydrofuran, rt, 18 h; (B) same as (A), reaction conducted at 60 °C, 18 h; (C) 2.2 equiv RB(OH)$_2$, 0.05 equiv PdCl$_2$(dppf), 4.0 equiv aq Na$_2$CO$_3$, 1,4-dioxane, 70 °C, 18 h; (D) 1.2 equiv RB(OH)$_2$, 1.5 equiv NaOtBu, 0.05 equiv PEPPSI-*i*Pr, 1,4-dioxane 80 °C, 18 h.

[a] Not detected by LC–MS.

[b] Yield estimated by LC–MS.

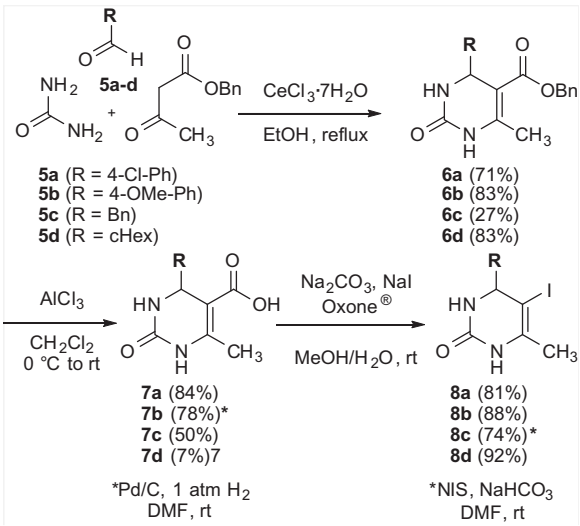
The first cross-coupling method tested on the 5-halo DHPMs **3** was the Suzuki–Miyaura reaction, which was chosen for its well-developed protocols and for the vast number of boronic acids and esters available for building structurally diverse analogs (Table 1). Several Suzuki coupling protocols (A–D) were screened for this preliminary investigation and the best of these unoptimized results are summarized in Table 1.

In general, aryl boronic acids are coupled adequately with DHPMs (**3a–b**) in either anhydrous or aqueous conditions.[18] However, sterically hindered or electron-deficient aryl boronic acids gave generally inferior results (Table 1, entries 12–16) and in some cases failed to yield any significant amount of products (Table 1, entries 7 and 8).

Conditions A and B (alkyl phosphine ligand in anhydrous tetrahydrofuran with potassium fluoride base, rt and 60 °C, respectively) gave good to excellent yields with electron-rich and electron-neutral aryl boronic acid substrates without steric hinderance (Table 1, entries 1, 2, 5, 6, 9–11). Condition C (dppf ligand in 1,4-dioxane with aqueous sodium carbonate) gave inferior results for phenyl boronic acid (Table 1, entry 3), but gave an improved result for the electron-deficient 4-fluorophenyl boronic acid (Table 1, entries 14 and 15 versus 12 and 13). Condition D (*N*-heterocyclic carbene ligand in 1,4-dioxane with sodium *tert*-butoxide base) failed to give any detectable products (Table 1, entry 4).

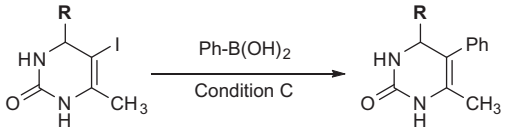
Pyridyl and vinyl boronic acids could also be coupled in moderate yields (Table 1, entries 17 and 18). The two different DHPM halides, iodide **3b** and bromide **3a**, gave results comparable to one another (Table 1, entries 1 and 2, 14 and 15).

Encouraged by these results, DHPM iodides **8a–d** with varied substituents at the C-4 position (substituted aryl, benzyl, and alkyl) were synthesized (Scheme 2). The effect of scaffold modification on the cross-coupling reaction was then examined (Table 2).



Scheme 2.

Table 2
Suzuki–Miyaura reactions of 5-iodo-DHPMs with varied substitution at C-4



8a-d **9a-d**

Entry	R	Halide	Isolated yield (%), **9**
1	4-Cl-Ph	**8a**	68
2	4-OMe-Ph	**8b**	81
3	Bn	**8c**	46
4	*c*Hex	**8d**	49

Condition C: 2.2 equiv $RB(OH)_2$, 0.05 equiv $PdCl_2$(dppf), 4.0 equiv aq. Na_2CO_3, 1,4-dioxane, 70 °C, 8–18 h.

The new DHPM halides **8a**–**d** were coupled with phenyl boronic acid using protocol C from Table 1. Both iodide **8a** with an electron-withdrawing substituent and iodide **8b** with an electron-donating substituent gave results similar to the unsubstituted phenyl scaffold (Table 2, entries 1 and 2, compared to 67% yield for **3b**). The benzyl- and alkyl-substituted compounds **8c**–**d** also coupled successfully but with diminished yields compared to the C-4 aryl compounds (Table 2, entries 3 and 4). These examples demonstrate that the Suzuki–Miyaura reaction can tolerate a fair range of variability at the C-4 position.

In conclusion, a novel synthesis of 5-substituted DHPMs **4, 9** via the Suzuki–Miyaura reaction with 5-halo DHPMs **3**, and **8** has been developed. This initial investigation demonstrates the utility of this approach for installing diversity at the C-5 position of the DHPM scaffold. Further development of this Suzuki reaction for a wider range of substrates, including organotrifluoroborates, is ongoing. The application of 5-halo DHPMs to additional cross-coupling reactions, such as the Heck, Stille, Sonogashira, and Buchwald/Hartwig reactions, is also under active examination.

Acknowledgments

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13. Reference for the palladium catalyzed deprotection of **1**: Desai, B.; Dallinger, D.; Oliver Kappe, C. O. *Tetrahedron* **2006** *62*, 4651. *Representative procedure for the synthesis of* **2**: aluminum trichloride (11.11 g, 83.54 mmol) was added to a stirred, ice-cooled mixture of benzyl ester **1** (13.45 g, 41.77 mmol) in methylene chloride (400 mL) under a dry nitrogen atmosphere. The reaction was removed from the ice-bath after 1 h and allowed to warm to rt. After 3 h the mixture was again cooled by ice-bath, 1 N aqueous hydrochloric acid (150 mL) was added, followed by diethyl ether (100 mL), and the mixture was stirred for 10 min. The mixture was filtered, rinsed with additional 1 N aqueous HCl (300 mL), diethyl ether (300 mL), and dried under high vacuum. The crude product was dissolved in 2 N aqueous sodium hydroxide (175 mL), filtered, cooled in an ice-bath, and the pH was adjusted to 5 with concd hydrochloric acid. Filtration of the resultant precipitate, followed by a water wash and drying under high vacuum gave **2** (9.10 g, 94% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.07 (s, 1H), 7.68 (s, 1H), 7.40–7.20 (m, 5H), 5.12 (s, 1H), 2.27 (s, 3H).
14. (a) Lee, K. J.; Lim, K. W.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 549; (b) *Representative procedure for the synthesis of* **3b**: Carboxylic acid **2** (232 mg, 1.0 mmol), sodium iodide (750 mg, 5.0 mmol), and sodium carbonate (106 mg, 1.0 mmol) were combined in a mixture of water (8 mL) and methanol (8 mL). Stirring and sonication gave a clear, colorless solution to which was added Oxone® (431 mg, 0.7 mmol). The now bright orange solution was protected from light and stirred at room temperature for 20 min. Filtration of the resultant solid, followed by a water wash, and drying under high vacuum gave **3b** (195 mg, 89% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.76 (s, 1H), 7.44–7.20 (m, 6H), 4.93 (s, 1H), 1.95 (s, 3H); ESI-MS *m*/*z* 315 $[M+H]^+$. Synthesis of **3a**: same as the above procedure with sodium bromide in place of sodium iodide. Note: some bromination of 6-methyl position was observed when greater equivalents of Oxone® were used.; Reference for bromination of DMPM 6-methyl position: (c) Khanetskyy, B.; Dallinger, D.; Oliver Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884.
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18. *Representative procedures for the* Suzuki–Miyaura *coupling* (Table 1, entry 9, Method A): Bromide **3a** (106 mg, 0.40 mmol), 4-methoxyphenyl boronic acid (122 mg, 0.80 mmol), bis(tri-*t*-butylphosphine)palladium (10 mg, 0.02 mmol), tris(dibenzylideneacetone)dipalladium (9 mg, 0.01 mmol), potassium fluoride (116 mg, 2.0 mmol), and tetrahydrofuran (2 mL) were combined in a sealed vial. The mixture was purged with nitrogen for several minutes and stirred for 15 h at room temperature. The reaction was concentrated under reduced pressure and purified by flash chromatography (silica gel, 100% ethyl acetate) to yield the aryl product **4** as a white solid (101 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.11 (m, 5H), 6.85 (d, 2H, J = 6.6 Hz), 6.76 (d, 2H, J = 6.8 Hz), 6.32 (s, 1H), 5.22 (s, 1H), 5.12 (s, 1H), 3.76 (s, 3H), 1.76 (s, 3H); ESI-MS *m*/*z* 295 $[M+H]^+$ (Table 1, entry 15, Method C): Iodide **3b** (63 mg, 0.20 mmol), 4-fluorophenyl boronic acid (62 mg, 0.44 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium dichloride (7 mg, 0.01 mmol), and dry 1,4-dioxane (1 mL) were combined in a sealed vial, stirred, and purged with nitrogen for several minutes. A solution of sodium carbonate (85 mg, 0.80 mmol) in water (1 mL) was added, the vial resealed, purged again with nitrogen for several minutes and then heated at 70 °C for 14 h while stirring. The reaction mixture was cooled, diluted with satd brine solution (5 mL), and extracted with ethyl acetate (10 mL). The ethyl acetate solution was dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 0–5% methanol/methylene chloride) to yield the aryl product **4** as a tan solid (30 mg, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 3H), 7.17–7.12 (m, 2H), 6.95–6.85 (m, 4H), 6.47 (s, 1H), 5.23 (s, 1H), 5.11 (s, 1H) 1.77 (s, 3H); ESI-MS *m*/*z* 283 $[M+H]^+$.