SYNTHESIS AND SUBSTITUTION REACTIONS OF 4(6)-CHLORO-DIHYDROPYRIMIDINES

Hidetsura Cho,*a,b Yoshizumi Yasui,c Satoshi Kobayashi,b Eunsang Kwon,a,d Mieko Arisawa,b and Masahiko Yamaguchi b,c

*a Graduate School of Science, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai, 980-8578, Japan. bGraduate School of Pharmaceutical Sciences, Tohoku University. cWPI Advanced Institute for Materials Research, Tohoku University. dResearch and Analytical Center for Giant Molecules, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai, 980-8578, Japan
E-mail: hcho@mail.pharm.tohoku.ac.jp

Abstract – Chlorination of the corresponding ketones with phenylphosphonic dichloride (PhPOCl₂) provided ethyl 6(4)-chloro-2-methyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate in good yield. The cross-coupling reactions of organoboronic acids or triethylborane with 1-tert-butyl 5-ethyl 4-chloro-2-methyl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate synthesized by regiospecific alkoxy carbonylation of the chlorinated dihydropyrimidine afforded 1,4(3,4)-dihydropyrimidines having a variety of functional groups at position-6(4) in good to excellent yields.

INTRODUCTION

Dihydropyrimidine (DP) could theoretically be represented as nine isomers including tautomers when it bears different substituted groups. Moreover, DPs in some cases are spontaneously oxidized during isolation or storage. Therefore, they are unstable and sometimes difficult to handle. We reported nucleophilic substitution at position-2 of 4-unsubstituted dihydropyrimidines A and B. Survey of the literature reveals no report on synthesis of C having phenyl, alkyl, and aralkyl groups by substitution of a chloro atom at position-4(6) of D. Recently, Zych has reported the synthesis of E by the Suzuki-Miyaura cross-coupling reaction of 5-halo-3,4-dihydropyrimidin-2(1H)-ones F, which were given by reaction at
position-5 of carboxylic acid $G$ with oxone and sodium halide in basic aqueous methanol.\textsuperscript{4} The report prompted us to disclose the first synthesis of various dihydropyrimidines $H$ (and $C$) by the cross-coupling reaction at position-4(6) of dihydropyrimidine $D$ with organoboronic acids or organoborane. It was expected that the skeleton $I$ could be constructed by chlorination\textsuperscript{5} of $J$\textsuperscript{5} and that successive regiospecific alkoxy-carbonylation developed by Cho\textsuperscript{1c,1d} could provide compound $D$. Alternatively, cyclization of

![Chemical structures]

**Figure 1.** A variety of dihydropyrimidines

amidines with compounds $K$ having an alkyl or a phenyl group at $R^5$ should afford cyclized compounds, while cyclization of amidines with unknown compounds $L$ having a trans-2-phenylvinyl or a vinyl group might give complicated compounds because of two reaction positions $a$ and $b$ of $L$. Therefore, development of a new procedure for modification at position-4(6) of dihydropyrimidines $D$ or $I$ would be useful and convenient to obtain various new DPs $C$ and $H$. 
Herein, we wish to disclose results of transformations using phenylphosphonic dichloride (PhPOCl$_2$) or POCl$_3$ from J to I and successive substitutions at position-4(6) of D or I with organoboronic acids or triethylborane.

RESULTS AND DISCUSSION

Treatment of benzaldehyde with 1.2 equivalents of diethyl malonate in the presence of 0.05 equivalents of piperidine and 0.025 equivalents of benzoic acid afforded the α, β-unsaturated carbonyl compound in 85% yield, which was heated at reflux with 1.2 equivalents of acetamidine hydrochloride in 2 equivalents of NaOEt in EtOH for 2 h to yield a single compound (trans: $J$=11.2 Hz), 5-ethyl 2-methyl-6-phenyl-1,4,5,6-tetrahydropyrimidin-4-one-5-carboxylate 1 in 67% yield.$^5$ Generally, it is difficult to maintain chlorinated dihydroheterocycles even under argon atmosphere. According to the literature,$^{sa}$-sb chlorination of dihydropyrazinones M, dihydropyridazinones N, dihydropyrimidin-2-ones O, or dihydropyridines P with POCl$_3$ did not give dihydroheterocycles because of over-chlorination and dehydrochlorination, but yielded aromatized heterocycles m, n-1, n-2, or p, respectively (Figure 2).

However, we obtained 4(6)-chloro-1,4(6)-dihydropyrimidine 2 using excess phenylphosphonic dichloride (PhPOCl$_2$) (110 °C, for 5 h) as well as 5 equivalents of POCl$_3$ (110 °C, for 4 h) in 60% yield.

![Figure 2. Unsuccessful chlorination of various dihydroheterocycles](image)

Alkoxycarbonylation of the sodium salt of 2 (prepared with 60% NaH) with 2 equivalents of di-tert-butyl dicarbonate (Boc$_2$O) regiospecifically furnished the sole compound 3 in 86% yield.$^{1c,1d}$ The chemical structure of 3 was determined by NMR analysis (HMBC and NOE). Thus, the regiospecificity of Boc protection was confirmed by three-bond long-range coupling (hetero-nuclear multiple bond connectivity: HMBC) between methine protons at position-6 and the carbonyl carbon of the Boc group. Also, when the protons of the t-Bu group ($\delta$= 1.55) of 3 were irradiated, a positive NOE (0.6%) was observed at H-4 ($\delta$=...
Suzuki-Miyaura cross-coupling reaction at position-4 of 3 with organoboronic acids or triethylborane was carried out. Thus, the reaction of dihydropyrimidine 3 and 1.5 equivalents of phenylboronic acid with either bis(triphenylphosphine)nickel (II) dichloride; \( \text{NiCl}_2(\text{PPh}_3)_2 \), tetrakis(triphenylphosphine)palladium(0); \( \text{Pd} (\text{PPh}_3)_4 \), or bis(triphenylphosphine)palladium (II) dichloride; \( \text{PdCl}_2(\text{PPh}_3)_2 \) was examined in the presence of 2 equivalents of \( \text{Cs}_2\text{CO}_3 \) or \( \text{K}_2\text{CO}_3 \) in THF or \( N, N \)-dimethylacetamide (DMA), respectively (Table 1).

![Figure 3. Dihydropyrimidines 1-5](image)

**Table 1. Optimization of the Cross Coupling Reaction at Position-4 of Dihydropyrimidine 3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol% NiCl(_2)(PPh(_3)_2)</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>THF</td>
<td>reflux</td>
<td>5</td>
<td>0 (82)(^a)</td>
</tr>
<tr>
<td>2</td>
<td>5 mol% Pd(_4)(PPh(_3))(_4)</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>THF</td>
<td>reflux</td>
<td>3</td>
<td>4 (63)</td>
</tr>
<tr>
<td>3</td>
<td>5 mol% PdCl(_2)(PPh(_3))(_2)</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>THF</td>
<td>reflux</td>
<td>3</td>
<td>34 (58)</td>
</tr>
<tr>
<td>4</td>
<td>5 mol% PdCl(_2)(PPh(_3))(_2)</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>DMA</td>
<td>60</td>
<td>4</td>
<td>85 (0)</td>
</tr>
<tr>
<td>5</td>
<td>5 mol% PdCl(_2)(PPh(_3))(_2)</td>
<td>( \text{K}_2\text{CO}_3 )</td>
<td>DMA</td>
<td>60</td>
<td>4</td>
<td>62 (25)</td>
</tr>
</tbody>
</table>

\(^a\) The values in parentheses show the recovered yield of compound 3.
Initially, the reaction of 3 with phenylboronic acid did not occur under conditions of 5 mol% NiCl$_2$(PPh$_3$)$_2$ and 2 equivalents of Cs$_2$CO$_3$ in THF at reflux for 5 h, but resulted in recovery of the starting material (Table 1, Entry 1). Changing the catalyst to Pd (PPh$_3$)$_4$, 4a was obtained in a poor yield (Entry 2). Using 5 mol% PdCl$_2$(PPh$_3$)$_2$, the cross-coupling reaction of 3 with 1.5 equivalents of phenylboronic acid was carried out to afford compound 4a in a modest yield (Entry 3). Subsequently, the solvent was replaced with DMA. Thus, treatment of 3 with 1.5 equivalents of phenylboronic acid in the presence of 5 mol% PdCl$_2$(PPh$_3$)$_2$ and 2 equivalents of Cs$_2$CO$_3$ in DMA at 60 °C provided dihydropyrimidine 4a in 85% yield (Entry 4). As the base, K$_2$CO$_3$ was employed instead of Cs$_2$CO$_3$ under the same reaction conditions as entry 4. The yield, however, was lower than that of the reaction using Cs$_2$CO$_3$ (Entry 5). Therefore, PdCl$_2$(PPh$_3$)$_2$ was selected as the catalyst for the other substrates. Thus, the reactions using the organoboronic acids with electron-donating or electron-withdrawing groups on a phenyl ring were studied. The reaction of 3 with o-tolylboronic acid in the presence of 5 mol% PdCl$_2$(PPh$_3$)$_2$ unsatisfactorily proceeded to give 4b contaminated with a small amount of the starting material recovered, because it is not easy to separate both starting material 3 and compound 4b by silica gel column chromatography. This may be due to lower reactivity because of steric hindrance of the methyl group of o-tolylboronic acid.

**Table 2. Cross Coupling Reaction of Dihydropyrimidines at Position-4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reagent</th>
<th>Time (h)</th>
<th>Compound 4</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$</td>
<td>C$_6$H$_5$B(OH)$_2$</td>
<td>4</td>
<td>4a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>C$_6$H$_4$Me-2</td>
<td>2-MeC$_6$H$_4$B(OH)$_2$</td>
<td>6</td>
<td>4b</td>
<td>99$^a$</td>
</tr>
<tr>
<td>3</td>
<td>C$_6$H$_4$OME-4</td>
<td>4-MeOC$_6$H$_4$B(OH)$_2$</td>
<td>3</td>
<td>4c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>C$_6$H$_4$NO$_2$-4</td>
<td>4-NO$_2$C$_6$H$_4$B(OH)$_2$</td>
<td>6</td>
<td>4d</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$H$_5$</td>
<td>C$_6$H$_5$B(OH)$_2$</td>
<td>4</td>
<td>4e</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>Et$_2$B</td>
<td>4</td>
<td>4f</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>S</td>
<td>S-B(OH)$_2$</td>
<td>4</td>
<td>4g</td>
<td>91</td>
</tr>
</tbody>
</table>

$^a$ 10 mol% of PdCl$_2$(PPh$_3$)$_2$, 3 eq. of organoboronic acid, 4 eq. of Cs$_2$CO$_3$.

Therefore, we employed 10 mol% catalyst to consume the starting material and to complete the reaction. Thus, compound 4b was obtained quantitatively using 10 mol% PdCl$_2$(PPh$_3$)$_2$ (Table 2, Entry 2). The reaction of 3 with 4-methoxyphenylboronic acid having an electron-donating group (OMe) furnished
product 4e in excellent yield (Table 2, Entry 3), but the yield of 4d was 69% in the case of an electron-withdrawing group (NO₂) (Entry 4). The remarkable result was found that dihydropyrimidine 4e having a trans-2-phenylvinyl group at position-4 was provided in 90% yield, which might not be given by the alternative cyclization reaction (Entry 5). Introduction of an ethyl group was carried out using ethylboronic acid, but 4f was not obtained. Therefore, other reaction conditions were examined using triethylborane, and 4f was provided in 83% yield (Entry 6). Regarding introduction of a heterocyclic moiety, for instance, a thienyl group, the cross-coupling reaction of 3 with 3-thienylboronic acid was performed to furnish 4g in 91% yield (Entry 7).

Table 3. Deprotection of dihydropyrimidine 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Compound 5</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>5a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₄Me-2</td>
<td>5b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₄OMe-4</td>
<td>5c</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₄NO₂-4</td>
<td>5d</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>-CH₂C₆H₅</td>
<td>5e</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>5f</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>-S</td>
<td>5g</td>
<td>93</td>
</tr>
</tbody>
</table>

Subsequently, deprotection of a Boc group was performed under the reaction conditions of CF₃COOH (TFA)-CH₂Cl₂ at rt for 1 h. Dihydropyrimidines 5a-5g were obtained in good yields.

On the other hand, to obtain compound 5 directly, the cross-coupling reaction of 2 with phenylboronic acid in the presence of 5 mol% PdCl₂(PPh₃)₂ was carried out, but product 5 was not obtained and the starting material was recovered, although the reason is unclear.

In summary, substitution of 1-tert-butyl 5-ethyl 4-chloro-2-methyl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate 3 synthesized from the corresponding ketone and phenylphosphonic dichloride (PhPOCl₂) was performed with organoboronic acids or organoborane to afford dihydropyrimidines 4 having a variety of moieties at position-4 in good yields. Deprotection of 4 with TFA provided various 5-ethyl 6(4)-substituted-2-methyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylates 5, which may be useful for biological applications. In addition, the cross-coupling reaction at position-4 should be useful.
because it can be applied to synthesize other dihydropyrimidines having various functional groups at position-2, 4(6), or -5.

**EXPERIMENTAL**

**General:** Unless otherwise noted, reactions were performed under argon. Melting points were determined on a Yanaco micro melting point apparatus and uncorrected. IR spectra were measured on a SHIMADZU FTIR-8300 spectrometer. $^1$H-NMR spectra were recorded on a Varian Mercury (400 MHz) or a Bruker AVANCE III 600 (600 MHz) with tetramethylsilane (0 ppm), CD$_3$OD (3.30 ppm), CD$_3$CN (1.93 ppm), or DMSO-$d_6$ (2.49 ppm) as an internal standard. The abbreviations of signal patterns are follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. $^{13}$C-NMR spectra were recorded on a Varian Mercury (400 MHz) or a Bruker AVANCE III 600 (600 MHz) with CDCl$_3$ (77.0 ppm), CD$_3$OD (49.0 ppm), CD$_3$CN (1.30 ppm), or DMSO-$d_6$ (39.7 ppm) as an internal standard. Mass spectra were recorded on a JMS-DX303, JMS-700, or JMS-T100GC spectrometer. Flash column chromatography was performed on silica gel 60N (Kanto, 40-60 mm) using the indicated solvent. Reactions and chromatography fractions were monitored with pre-coated silica gel 60 F$_{254}$ plates (Merck).

**Ethyl 6(4)-chloro-2-methyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (2):** A mixture of ethyl 2-methyl-4-phenyl-1,4,5,6-tetrahydropyrimidin-6-one-5-carboxylate 1 (633 mg, 2.43 mmol) and phenylphosphonic dichloride (5 mL, 35.26 mmol) was heated at 110 °C for 5 h. The reaction mixture was poured into ice-cooled saturated aqueous NaHCO$_3$. After adding aqueous 2M NaOH, the organic materials were extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc) to give chloride 2 (406 mg, 60%) as yellow crystals; mp 155-156 °C (Et$_2$O); IR (KBr) 2979, 2846, 1682, 1604, 1514, 1323, 1250, 1117 cm$^{-1}$; $^1$H-NMR (400 MHz, CD$_3$OD) $\delta$ 1.11 (3H, t, $J$ = 7.2 Hz), 1.98 (3H, s), 3.97–4.09 (2H, m), 5.55 (1H, s), 7.27-7.37 (5H, m); $^{13}$C-NMR (100 MHz, CD$_3$OD) $\delta$ 14.4, 20.9, 57.1, 61.4, 102.8, 127.9, 129.5, 129.9, 145.4, 148.7, 161.9, 166.1; LRMS (EI) $m/z$ 278 (M$^+$); HRMS (EI) $m/z$ Calcd for C$_{14}$H$_{15}$ClN$_2$O$_2$ (M$^+$) 278.0822, Found: 278.0820.

**1-tert-Butyl 5-ethyl 4-chloro-2-methyl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (3):** To sodium hydride (60% dispersion in mineral oil, 89.4 mg, 2.24 mmol) was added a solution of 2 (406 mg, 1.46 mmol) in DMF (5 mL) and a solution of di-tert-butyl dicarbonate (645 mg, 2.96 mmol) in DMF (3 mL) at 0 °C. After stirring for 30 min at rt, water was added and the organic materials were extracted with toluene. The combined organic extracts were washed with water and brine, dried over Na$_2$SO$_4$, and
concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:toluene:EtOAc = 50:50:0 → 50:48:2) to give the carbamate 3 (474 mg, 86%) as pale yellow crystals; mp 106-107 °C (n-hexane-Et2O); IR (KBr) 2981, 1724, 1693, 1558, 1369, 1230, 1151, 1091 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.25 (3H, t, J = 7.2 Hz), 1.55 (9 H, s), 2.42 (3H, s), 4.13-4.26 (2H, m), 6.26 (1H, s), 7.31 (5H, brs); ¹³C-NMR (100 MHz, CDCl₃) δ 14.0, 25.7, 28.0, 55.7, 61.1, 84.8, 111.5, 126.9, 128.6, 128.7, 139.2, 143.5, 151.3, 158.4, 163.7; LRMS (EI) m/z Calcd for C₁₉H₂₃ClN₂O₄ (M⁺) 378.1346, Found: 378.1339.

I-tert-Butyl 5-ethyl 2-methyl-4,6-diphenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4a): A solution of 3 (46.2 mg, 0.122 mmol), phenylboronic acid (22.1 mg, 0.181 mmol), bis(triphenylphosphine)-palladium(II) dichloride PdCl₂(PPh₃)₂ (4.5 mg, 0.0064 mmol), and Cs₂CO₃ (81.3 mg, 0.249 mmol) in DMA (2 mL) was carefully degassed three times with freeze-pump-thaw cycles under argon atmosphere and heated for 4 h at 60 °C. The reaction mixture was diluted with water and the organic materials were extracted with toluene. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the residue, which was purified by silica gel column chromatography (toluene:EtOAc = 10:0 → 97:3) to afford compound 4a (43.5 mg, 85%); pale yellow crystals (needles); mp 96-97 °C (CHCl₃); IR (KBr) 2979, 2933, 1707, 1572, 1371, 1230, 1138, 1032 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.894 (3H, t, J = 7.2 Hz), 1.57 (9H, s), 2.41 (3H, s), 3.87-4.02 (2H, m), 6.30 (1H, s), 7.28-7.39 (8H, m), 7.49-7.51 (2H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 13.5, 25.6, 28.1, 54.3, 60.5, 83.8, 114.3, 127.1, 127.8, 128.2, 128.53, 128.58, 128.64. 137.9, 139.6, 151.0, 151.9, 154.9, 166.3. LRMS (EI) m/z 420 (M⁺); HRMS (EI) m/z Calcd for C₂₅H₂₈N₂O₄ (M⁺) 420.2049, Found: 420.2053.

1-tert-Butyl 5-ethyl 2-methyl-6-phenyl-4-o-tolyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4b): A solution of 3 (45.0 mg, 0.119 mmol), o-tolylboronic acid (48.5 mg, 0.357 mmol), PdCl₂(PPh₃)₂ (8.39 mg, 0.0120 mmol) and Cs₂CO₃ (156 mg, 0.479 mmol) in DMA (2.5 mL) was degassed three times with freeze-pump-thaw cycles under argon atmosphere and heated for 6 h at 60 °C. Water was added to the reaction mixture and the organic materials were extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:EtOAc = 10:0 → 9:1) to give compound 4b (51.1 mg, 99%) as a colorless oil. IR (neat) 2979, 1720, 1566, 1493, 1369, 1230, 1153, 1095 cm⁻¹; ¹H-NMR (400 MHz, CD₃CN) δ 0.790 (3H, t, J = 7.2 Hz), 1.56 (9H, s), 2.24 (3H, brs), 2.34 (3H, s), 3.77-3.91 (2H, m), 6.26 (1H, s), 7.07-7.41 (9H, m); ¹³C-NMR (100 MHz, CD₃CN) δ 13.8, 19.6, 25.8, 28.2, 54.5, 61.2, 84.9, 116.0, 126.2, 127.7, 128.7, 128.7, 129.3, 129.7, 130.5, 136.5, 139.7, 141.1,
152.8, 153.0, 156.2, 166.3; LRMS (EI) m/z 434 (M⁺); HRMS (EI) m/z Calcd for C₂₆H₃₀N₂O₄ (M⁺) 434.2206, Found: 434.2197.

1-tert-Butyl 5-ethyl 4-aryl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4c): pale yellow crystals; mp 57-58 °C (CHCl₃); IR (KBr) 2979, 2833, 1707, 1574, 1371, 1248, 1034 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.97 (3H, t, J = 7.2 Hz), 1.56 (9H, s), 2.39 (3H, s), 3.83 (3H, s), 3.91-4.06 (2H, m), 6.28 (1H, s), 6.89-6.92 (2H, m), 7.25-7.38 (5H, m), 7.48-7.51 (2H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 13.7, 25.5, 28.1, 54.4, 55.3, 60.5, 83.6, 113.2, 113.2, 127.1, 128.2, 128.6, 129.8, 130.3, 139.8, 150.6, 151.9, 154.5, 166.5; LRMS (EI) m/z 450  (M⁺); HRMS (EI) m/z Calcd for C₂₆H₃₀N₂O₄ (M⁺) 450.2155, Found: 450.2162.

1-tert-Butyl 5-ethyl 2-methyl-4-aryl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4d): yellow crystals; mp 97-98 °C (CHCl₃); IR (KBr) 3068, 2974, 2939, 1714, 1525, 1348, 1232 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.2 Hz), 1.58 (9H, s), 2.43 (3H, s), 3.93-4.02 (2H, m), 6.31 (1H, s), 7.29-7.38 (5H, m), 7.65-7.67 (2H, m), 8.23-8.26 (2H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 13.6, 25.7, 28.1, 54.3, 60.9, 84.3, 115.7, 123.0, 127.0, 128.5, 128.8, 129.7, 139.2, 144.7, 147.7, 149.2, 151.7, 156.2, 165.3; LRMS (EI) m/z 465 (M⁺); HRMS (EI) m/z Calcd for C₂₅H₂₇N₃O₆ (M⁺) 465.1900, Found: 465.1931.

1-tert-Butyl 5-ethyl 2-methyl-6-phenyl-4-trans-styryl-1,6-dihydropyrimidine-1,5-dicarboxylate (4e): a yellow oil; IR (neat) 2979, 2933, 1720, 1620, 1369, 1238, 1153 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.26 (3H, t, J = 7.2 Hz), 1.56 (9H, s), 2.44 (3H, s), 4.15-4.27 (2H, m), 6.27 (1H, s), 7.25-7.37 (8H, m), 7.59-7.61 (2H, m), 7.76 (1H, d, J = 15.6 Hz), 8.22 (1H, d, J = 15.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 14.2, 25.7, 28.2, 53.8, 60.6, 83.6, 111.7, 123.3, 127.2, 127.6, 128.1, 128.5, 128.57, 128.62, 137.0, 137.3, 140.0, 148.1, 151.9, 155.5, 165.6; LRMS (EI) m/z 446 (M⁺); HRMS (EI) m/z Calcd for C₂₇H₃₀N₂O₄ (M⁺) 446.2206, Found: 446.2207.

1-tert-Butyl 5-ethyl 4-ethyl-2-methyl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4f): A solution of 3 (53.5 mg, 0.141 mmol), triethylborane (1 M in hexane, 0.200 mL, 0.200 mmol), PdCl₂(PPh₃)₂ (4.5 mg, 0.00642 mmol) and Cs₂CO₃ (95.2 mg, 0.292 mmol) in N, N-dimethylacetamide (2 mL) was degassed twice with freeze-pump-thaw cycles under argon atmosphere and heated for 4 h at 60 °C. The reaction mixture was diluted with water and the organic materials were extracted with toluene. The combined organic extracts were washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene:EtOAc =
10.0 → 97.3) to give compound 4f (43.7 mg, 83%); yellow crystals; mp 70-71 °C (CHCl₃); IR (KBr) 2979, 2935, 1730, 1577, 1225, 1099 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.22 (3H, t, J = 7.2 Hz), 1.23 (3H, t, J = 7.2 Hz), 1.56 (9H, s), 2.35 (3H, s), 2.71 (1H, dq, J = 7.2, 12.4 Hz), 2.88 (1H, dq, J = 7.2, 12.4 Hz), 4.09-4.21 (2H, m), 6.14 (1H, s), 7.23-7.30 (5H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 12.6, 14.1, 25.4, 27.1, 28.1, 53.3, 60.4, 83.6, 111.5, 127.0, 128.0, 128.4, 140.0, 151.9, 155.6, 157.1, 165.7; LRMS (EI) m/z 372 (M⁺); HRMS (EI) m/z Calcd for C₂₁H₂₈N₂O₄ (M⁺) 372.2049, Found: 372.2045.

1-tert-Butyl 5-ethyl 2-methyl-6-phenyl-4-(thiophen-3-yl)-1,6-dihydropyrimidine-1,5-dicarboxylate (4g): yellow crystals; 77-79 °C (CHCl₃); IR (KBr) 3093, 2979, 2933, 1702, 1574, 1230 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.05 (3H, t, J = 7.2 Hz), 1.56 (9H, s), 2.38 (3H, s), 3.99-4.12 (2H, m), 6.28 (1H, s), 7.25-7.38 (7H, m), 7.72 (1H, dd, J₁ = J₂ = 2.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 13.8, 25.5, 28.1, 54.4, 60.7, 83.7, 113.2, 124.3, 127.0, 127.1, 128.2, 128.5, 128.6, 138.0, 140.0, 145.4, 151.9, 154.8, 166.3; LRMS (EI) m/z 426 (M⁺); HRMS (EI) m/z Calcd for C₂₃H₂₆N₂O₄S (M⁺) 426.1613, Found: 426.1606.

Deprotection of 4 with trifluoroacetic acid: 5-Ethyl 2-methyl-4,6-diphenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5a): To a stirred solution of 4a (40.1 mg, 0.0955 mmol) in CH₂Cl₂ (1 mL) was added trifluoroacetic acid (0.75 mL, 10.1 mmol,) at 0 °C. Stirring was continued at room temperature for 1 h. The reaction mixture was basified with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, and concentrated under reduced pressure to leave the residue. Purification by silica gel column chromatography (n-hexane:EtOAc:MeOH = 8:2:0 → 0:95:5) provided compound 5a (29.4 mg, 96%); colorless crystals; mp 212-213 °C (n-hexane-Et₂O); IR (KBr) 3030, 2981, 2868, 2731, 1674, 1504, 1234, 1084, 966 cm⁻¹; ¹H-NMR (400 MHz, CD₂CN) δ 0.79 (3H, t, J = 7.2 Hz), 1.93 (3H, s), 3.76 (2H, q, J = 7.2 Hz), 5.50 (1H, s), 7.24-7.42 (10H, m); ¹³C-NMR (100 MHz, CD₂CN) δ 14.0, 21.4, 58.3, 60.0, 101.6, 128.0, 128.2, 128.7, 129.3, 129.4, 129.6, 138.4, 146.7, 150.1, 153.3, 167.5; LRMS (EI) m/z 320 (M⁺); HRMS (EI) m/z Calcd for C₂₀H₂₀N₂O₂ (M⁺) 320.1525, Found: 320.1526.

5-Ethyl 2-methyl-6(4)-(2-methyl)phenyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5b): colorless crystals; mp 200-201 °C (n-hexane-Et₂O); IR (KBr) 3163, 3033, 2898, 1678, 1496, 1371, 1338, 1082 cm⁻¹; ¹H-NMR (400 MHz, CD₂CN) δ 0.74 (3H, t, J = 7.2Hz), 0.74* (t, J = 7.2 Hz), 1.89* (s), 1.91 (3H, s), 2.23 (3H, s), 2.23* (s), 3.64–3.72 (2H, m), 3.64–3.72* (m), 5.51* (s), 5.54 (1H, s), 7.09-7.45 (9H, m), 7.09-7.45* (m); ¹³C-NMR (100 MHz, CD₂CN) δ 13.9, 13.9*, 19.2*, 19.5, 21.2*, 21.4, 58.5*, 59.1, 60.0, 60.0*, 101.8, 102.5*, 126.29*, 126.35, 128.0, 128.1*, 128.1, 128.1*, 128.6, 128.6*, 129.1, 129.1*, 129.3, 129.4*, 130.4, 130.5*, 136.1, 137.2*, 138.0, 138.0*, 146.9*, 147.2, 148.5, 149.2*, 152.3, 152.3*,
166.9*, 167.0; LRMS (EI) m/z 334 (M'); HRMS (EI) m/z Calcd for C_{21}H_{22}N_{2}O_{2} (M') 334.1681, Found: 334.1675. (Two isomers were observed in both {sup}{1}H-NMR and {sup}{13}C-NMR spectra, and the signals with a mark <*> indicate a minor isomer.)

5-Ethyl 2-methyl-6(4)-(4-methoxy)phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5c):
pale yellow crystals; mp 159-160 °C (n-hexane-Et_{2}O); IR (KBr) 3296, 3120, 3028, 2906, 2835, 1701, 1649, 1510, 1242, 1032 cm^{-1}; {sup}{1}H-NMR (400 MHz, CD_{2}CN) δ 0.85 (3H, t, J = 7.2 Hz), 1.92 (3H, s), 3.73-3.85 (2H, m), 3.80 (3H, s), 5.47 (1H, s), 6.90-6.92 (2H, m), 7.24-7.41 (7H, m); {sup}{13}C-NMR (100 MHz, CD_{2}CN) δ 14.1, 21.4, 56.0, 58.6, 60.2, 100.6, 114.0, 128.0, 128.1, 129.4, 130.1, 131.0, 146.8, 149.6, 152.9, 161.2, 167.7; LRMS (EI) m/z 350 (M'); HRMS (EI) m/z Calcd for C_{21}H_{22}N_{2}O_{3} (M') 350.1630, Found: 350.1615.

5-Ethyl 2-methyl-6(4)-(4-nitro)phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5d):
yellow crystals; 83-84 °C (n-hexane-Et_{2}O); IR (KBr) 3309, 2979, 1685, 1591, 1518, 1348, 1236, 1099 cm^{-1}; {sup}{1}H-NMR (400 MHz, CD_{2}CN) δ 0.79 (3H, t, J = 7.2 Hz), 1.94 (3H, s), 3.76 (2H, q, J = 7.2 Hz), 5.51 (1H, s), 7.27-7.43(5H, m), 7.53 (2H, d, J = 8.8 Hz), 8.18 (2H, d, J = 8.8 Hz); {sup}{13}C-NMR (100 MHz, CD_{2}CN) δ 13.9, 21.8, 56.3, 60.6, 104.4, 123.8, 127.9, 128.8, 129.6, 130.4, 146.2, 147.5, 148.5, 151.9, 157.0, 166.9; LRMS (EI) m/z 365 (M'); HRMS (EI) m/z Calcd for C_{20}H_{19}N_{3}O_{4} (M') 365.1376, Found: 365.1363.

5-Ethyl 2-methyl-6(4)-trans-styryl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5e):
yellow crystals; mp 155-157 °C (n-hexane-Et_{2}O); IR (KBr) 3386, 2979, 1685, 1618, 1589, 1552, 1493, 1219, 1049 cm^{-1}; {sup}{1}H-NMR (400 MHz, CD_{2}CN) δ 1.17 (3H, t, J = 7.2Hz), 2.01 (3H, s), 4.06 (2H, q, J = 7.2 Hz), 5.47 (1H, s), 7.22-7.56 (11H, m), 8.11 (1H, d, J = 15.6 Hz); {sup}{13}C-NMR (100 MHz, CD_{2}CN) 14.5, 22.2, 56.2, 60.8, 104.6, 124.8, 127.8, 128.2, 128.5, 129.50, 129.54, 129.9, 135.3, 137.9, 146.7, 148.9, 156.6, 167.5; LRMS (EI) m/z 346 (M'); HRMS (EI) m/z Calcd for C_{22}H_{12}N_{2}O_{2} (M') 346.1681, Found: 346.1669.

5-Ethyl 4(6)-ethyl-2-methyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5f):
colorless crystals (needles); mp 135-136 °C (n-hexane-AcOEt); IR (KBr) 3180, 3062, 3027, 2978, 2924, 2800, 1817 1685, 1510, 1456, 1248, 1109 cm^{-1}; {sup}{1}H-NMR (400 MHz, CDCl_{3}) δ 1.15 (3H, t, J = 7.2Hz), 1.22 (3H, t, J = 7.6 Hz), 1.97 (3H, s), 2.65-2.82 (2H, m), 4.02-4.08 (2H, m), 5.51 (1H, s), 7.20-7.33 (5H, m); {sup}{13}C-NMR (100 MHz, CDCl_{3}) δ 12.6, 14.1, 21.3, 26.0, 57.6, 59.6, 99.9, 127.1, 127.2, 128.4, 145.3, 151.4, 152.2, 166.4; LRMS (EI) m/z 272 (M'); HRMS (EI) m/z Calcd for C_{16}H_{20}N_{2}O_{2} (M') 272.1525, Found:
5-Ethyl 2-methyl-4(6)-phenyl-6(4)-(thiophen-3-yl)-1,4(6)-dihydropyrimidine-5-carboxylate (5g): pale yellow crystals; mp 167-168 °C (n-hexane-Et₂O); IR (KBr) 3107, 3030, 2981, 2850, 2723, 1672, 1495, 1236, 1086 cm⁻¹; ¹H-NMR (400 MHz, CD₃CN) δ 0.92 (3H, t, J = 7.2 Hz), 1.93 (3H, s), 3.79-3.90 (2H, m), 5.47 (1H, s), 7.12 (1H, dd, J = 1.6, 5.2 Hz), 7.23-7.40 (6H, m), 7.50 (1H, dd, J = 1.6, 3.2 Hz); ¹³C-NMR (100 MHz, CD₃CN) δ 14.1, 21.5, 58.3, 60.4, 101.8, 125.4, 126.5, 128.0, 128.2, 129.4, 129.7, 138.5, 144.8, 146.6, 153.6, 167.6; LRMS (EI) m/z 326 (M⁺). HRMS (EI) m/z Calcd for C₁₈H₁₈N₂Os₂ (M⁺) 326.1089, Found: 326.1074.

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REFERENCES AND NOTES