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

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Abstract – Chlorination of the corresponding ketones with phenylphosphonic dichloride ($PhPOCl_2$) 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 alkoxycarbonylation 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.[1] 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**.[2] 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[3] of 5-halo-3,4-dihydropyrimidin-2(1*H*)-ones **F**, which were given by reaction at

position-5 of carboxylic acid **G** with oxone and sodium halide in basic aqueous methanol.[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[5] of **J**[6] and that successive regiospecific alkoxycarbonylation developed by Cho[1c,1d] could provide compound **D**. Alternatively, cyclization of

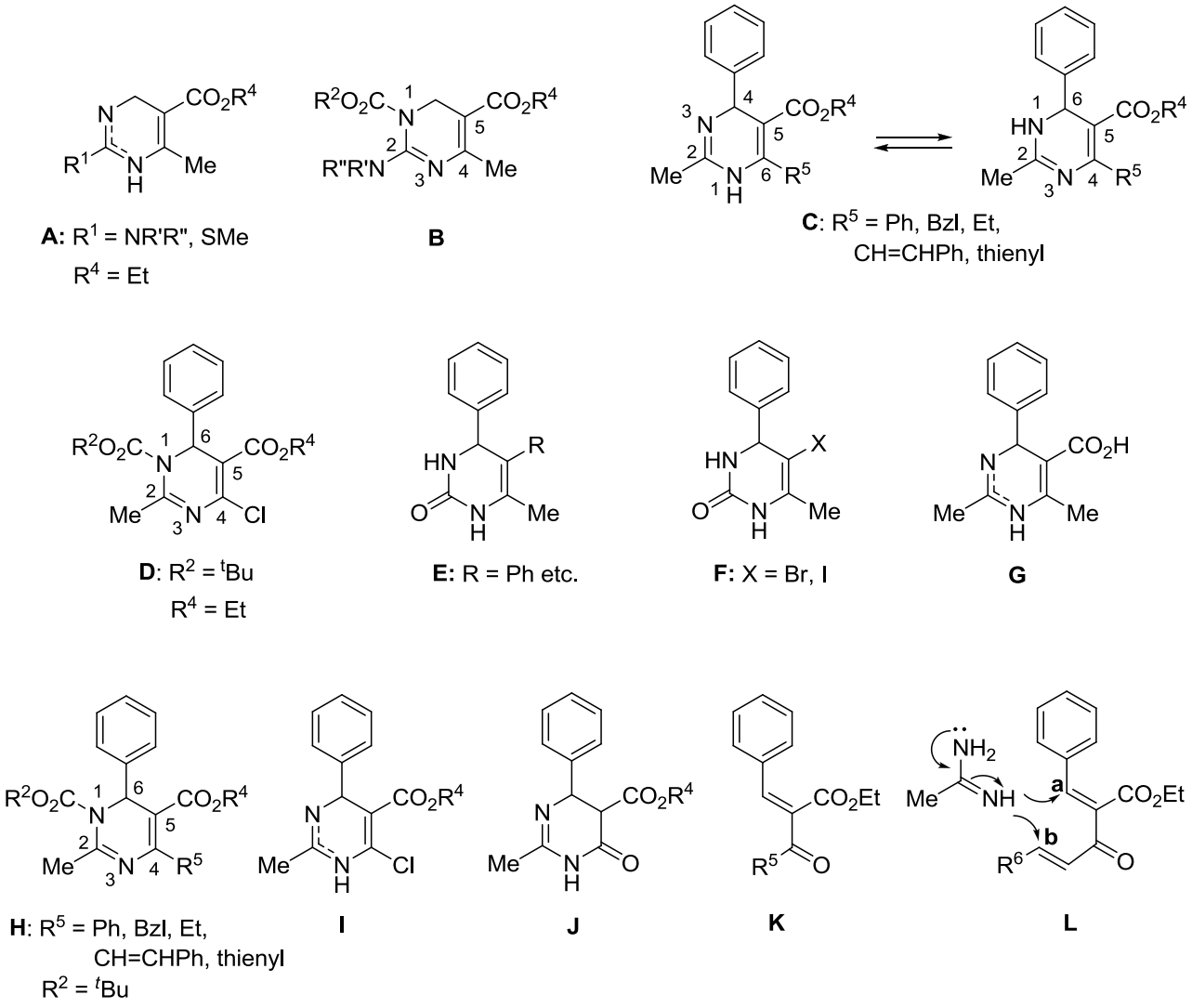


Figure 1. A variety of dihydropyrimidines

amidines with compounds **K** having an alkyl or a phenyl group at R^5should 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 postion-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.[6] Generally, it is difficult to maintain chlorinated dihydroheterocycles even under argon atmosphere. According to the literature,[5a,5b] 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.

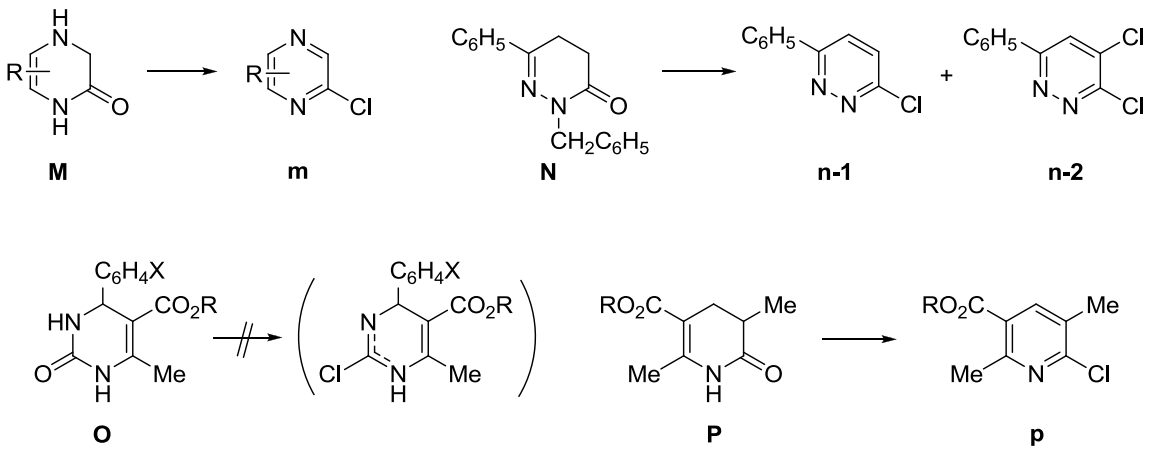


Figure 2. Unsuccessful chlorination of various dihydroheterocycles

Alkoxycarbonylation of the sodium salt of **2** (prepared with 60% NaH) with 2 equivalents of di-*tert*-butyl dicarbonate (Boc_2O) 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 (δ= 1.55) of **3** were irradiated, a positive NOE (0.6%) was observed at H-4 (δ=

6.26). 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

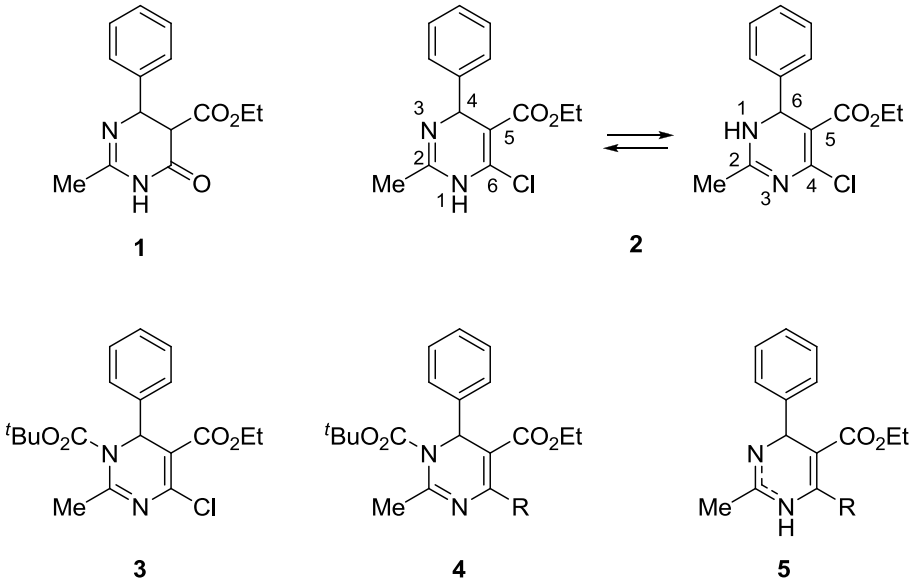
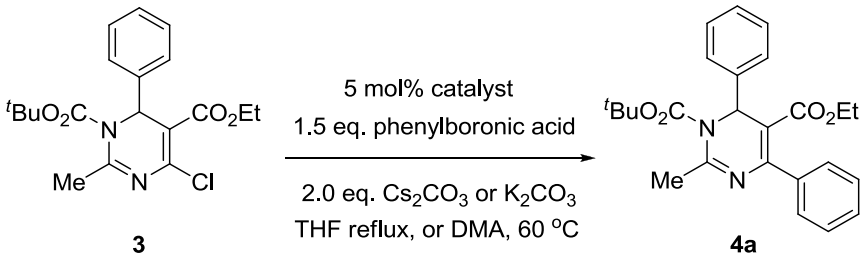


Figure 3. Dihydropyrimidines **1-5**

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



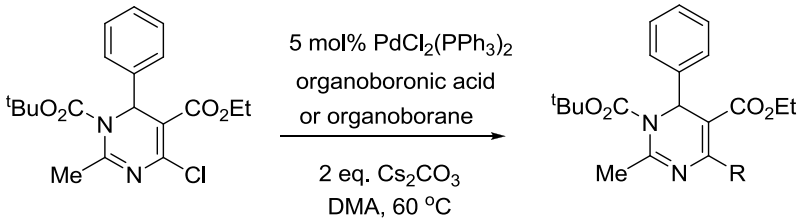
Entry	Catalyst	Base	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	5 mol% $NiCl_2(PPh_3)_2$	Cs_2CO_3	THF	reflux	5	0 (82)[a]
2	5 mol% $Pd(PPh_3)_4$	Cs_2CO_3	THF	reflux	3	4 (63)
3	5 mol% $PdCl_2(PPh_3)_2$	Cs_2CO_3	THF	reflux	3	34 (58)
4	5 mol% $PdCl_2(PPh_3)_2$	Cs_2CO_3	DMA	60	4	85 (0)
5	5 mol% $PdCl_2(PPh_3)_2$	K_2CO_3	DMA	60	4	62 (25)

[a] The values in parentheses show the recovered yield of compound **3**.

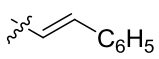
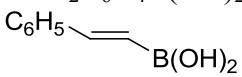
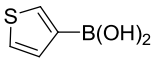
phenylboronic acid with either bis(triphenylphosphine)nickel (II) dichloride; $NiCl_2(PPh_3)_2$, tetrakis(triphenylphosphine)palladium(0); Pd $(PPh_3)_4$, or bis(triphenylphosphine)palladium (II) dichloride; $PdCl_2(PPh_3)_2$ was examined in the presence of 2 equivalents of Cs_2CO_3 or K_2CO_3 in THF or *N*, *N*-dimethylacetamide (DMA), respectively (Table 1).

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_2CO_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_2CO_3 in DMA at 60 ^oC provided dihydropyrimidine **4a** in 85% yield (Entry 4). As the base, K_2CO_3 was employed instead of Cs_2CO_3 under the same reaction conditions as entry 4. The yield, however, was lower than that of the reaction using Cs_2CO_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



4

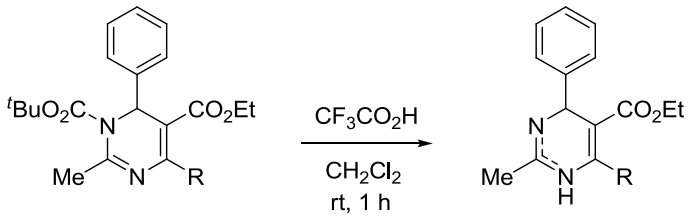
Entry	R	Reagent	Time (h)	Compound **4**	Yield (%)
1	C_6H_5	$C_6H_5B(OH)_2$	4	**4a**	85
2	C_6H_4Me-2	2-$MeC_6H_4B(OH)_2$	6	**4b**	99[a]
3	C_6H_4OMe-4	4-$MeOC_6H_4B(OH)_2$	3	**4c**	92
4	$C_6H_4NO_2$-4	4-$NO_2C_6H_4B(OH)_2$	6	**4d**	69
5			4	**4e**	90
6	Et	Et_3B	4	**4f**	83
7			4	**4g**	91

[a] 10 mol% of $PdCl_2(PPh_3)_2$, 3 eq. of organoboronic acid, 4 eq. of Cs_2CO_3.

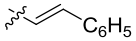
Therefore, we employed 10 mol% catalyst to consume the starting material and to complete the reaction. Thus, compound **4b** was obtained quantitatively using 10 mol% $PdCl_2(PPh_3)_2$ (Table 2, Entry 2). The reaction of **3** with 4-methoxyphenylboronic acid having an electron-donating group (OMe) furnished

product **4c** in excellent yield (Table 2, Entry 3), but the yield of **4d** was 69% in the case of an electron-withdrawing group (NO_2) (Entry 4). The remarkable result was found that dihydropyrimidine **4e** having a *trans*-2-phenylvinyl group at postion-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**



4 **5**

Entry	R	Compound **5**	Yield (%)
1	C_6H_5	**5a**	96
2	C_6H_4Me-2	**5b**	90
3	C_6H_4OMe-4	**5c**	86
4	$C_6H_4NO_2$-4	**5d**	89
5		**5e**	78
6	Et	**5f**	98
7		**5g**	93

Subsequently, deprotection of a Boc group was performed under the reaction conditions of CF_3COOH (TFA)-CH_2Cl_2 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% $PdCl_2(PPh_3)_2$ 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 ($PhPOCl_2$) 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_3OD (3.30 ppm), CD_3CN (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_3OD (49.0 ppm), CD_3CN (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 ^{o}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_2SO_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_2O); IR (KBr) 2979, 2846, 1682, 1604, 1514, 1323, 1250, 1117 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 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_3OD) δ 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 $C_{14}H_{15}ClN_2O_2$ (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 ^{o}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_2SO_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-Et_2O); IR (KBr) 2981, 1724, 1693, 1558, 1369, 1230, 1151, 1091 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, *J* = 7.2 Hz), 1.55 (9H, s), 2.42 (3H, s), 4.13–4.26 (2H, m), 6.26 (1H, s), 7.31 (5H, brs); ^{13}C-NMR (100 MHz, $CDCl_3$) 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* 378 (M^+); HRMS (EI) *m/z* Calcd for $C_{19}H_{23}ClN_2O_4$ (M^+) 378.1346, Found: 378.1339.

***1-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 $PdCl_2(PPh_3)_2$ (4.5 mg, 0.0064 mmol), and Cs_2CO_3 (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 ^{o}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 Na_2SO_4 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 ($CHCl_3$); IR (KBr) 2979, 2933, 1707, 1572, 1371, 1230, 1138, 1032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{28}N_2O_4$ (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), $PdCl_2(PPh_3)_2$ (8.39 mg, 0.0120 mmol) and Cs_2CO_3 (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 Na_2SO_4, 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}; ^{1}H-NMR (400 MHz, CD_3CN) 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); ^{13}C-NMR (100 MHz, CD_3CN) 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 $C_{26}H_{30}N_2O_4$ (M^+) 434.2206, Found: 434.2197.

1-*tert*-Butyl 5-ethyl 4-*p*-methoxyphenyl-2-methyl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4c): pale yellow crystals; mp 57-58 °C ($CHCl_3$); IR (KBr) 2979, 2833, 1707, 1574, 1371, 1248, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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, 160.2, 166.5; LRMS (EI) *m/z* 450 (M^+); HRMS (EI) *m/z* Calcd for $C_{26}H_{30}N_2O_5$ (M^+) 450.2155, Found: 450.2162.

1-*tert*-Butyl 5-ethyl 2-methyl-4-*p*-nitrophenyl-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (4d): yellow crystals; mp 97-98 °C ($CHCl_3$); IR (KBr) 3068, 2974, 2939, 1714, 1525, 1348, 1232 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{27}N_3O_6$ (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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{27}H_{30}N_2O_4$ (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), $PdCl_2(PPh_3)_2$ (4.5 mg, 0.00642 mmol) and Cs_2CO_3 (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 ^{o}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 Na_2SO_4, 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 ($CHCl_3$); IR (KBr) 2979, 2935, 1730, 1631, 1577, 1225, 1099 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{28}N_2O_4$ (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 ($CHCl_3$); IR (KBr) 3093, 2979, 2933, 1702, 1574, 1230 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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, $J_1 = J_2$ = 2.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{26}N_2O_4S$ (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 CH_2Cl_2 (1 mL) was added trifluroacetic 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 $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, 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-Et_2O); IR (KBr) 3030, 2981, 2868, 2731, 1674, 1504, 1234, 1084, 966 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN) 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); ^{13}C-NMR (100 MHz, CD_3CN) δ 14.0, 21.4, 58.3, 60.2, 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 $C_{20}H_{20}N_2O_2$ (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-Et_2O); IR (KBr) 3163, 3033, 2898, 1678, 1496, 1371, 1338, 1082 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN) δ 0.74 (3H, t, *J* = 7.2Hz), 0.74* (t, *J* = 7.2Hz), 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); ^{13}C-NMR (100 MHz, CD_3CN) 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 $C_{21}H_{22}N_2O_2$ (M^+) 334.1681, Found: 334.1675. (Two isomers were observed in both ^{1}H-NMR and ^{13}C-NMR spectra, and the signals with a mark <*> indicate a minor isomer.[2])

5-Ethyl 2-methyl-6(4)-(4-methoxy)phenyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5c): pale yellow crystals; mp 159-160 °C (*n*-hexane-Et_2O); IR (KBr) 3296, 3120, 3028, 2906, 2835, 1701, 1649, 1510, 1242, 1032cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN) 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); ^{13}C-NMR (100 MHz, CD_3CN) 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 $C_{21}H_{22}N_2O_3$ (M^+) 350.1630, Found: 350.1615.

5-Ethyl 2-methyl-6(4)-(4-nitro)phenyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (5d): yellow crystals; 83-84 °C (*n*-hexane-Et_2O); IR (KBr) 3309, 2979, 1685, 1591, 1518, 1348, 1236, 1099 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN) 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); ^{13}C-NMR (100 MHz, CD_3CN) 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 $C_{20}H_{19}N_3O_4$ (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_2O); IR (KBr) 3386, 2979, 1691, 1618, 1589, 1552, 1493, 1219, 1049 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN) δ 1.17 (3H, t, *J* = 7.2 Hz), 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); ^{13}C-NMR (100 MHz, CD_3CN) 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 $C_{22}H_{12}N_2O_2$ (M^+) 346.1681, Found: 346.1669.

5-Ethyl 6(4)-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, 1685, 1510, 1456, 1248, 1109 cm^{-1}; ^{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); ^{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 $C_{16}H_{20}N_2O_2$ (M^+) 272.1525, Found:

272.1514.

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-Et_2O); IR (KBr) 3107, 3030, 2981, 2850, 2723, 1672, 1495, 1236, 1086 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN) 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, 3.2Hz); ^{13}C-NMR (100 MHz, CD_3CN) 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 $C_{18}H_{18}N_2O_2S$ (M^+) 326.1089, Found: 326.1074.

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