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Synthesis of 4-unsubstituted dihydropyrimidines. Nucleophilic substitution at position-2 of dihydropyrimidines

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ABSTRACT

Synthesis of novel 4-unsubstituted dihydropyrimidines (DPs) was performed. Subsequently, a variety of 4-unsubstituted 1,4(3,4)-DPs with amino moieties at position-2 were obtained in excellent yields by activation of position-2 owing to regioselective alkoxycarbonylation at position-3 of the DP skeleton. 3-Oxo-2-phenyl-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrimidine was obtained using phenylhydrazine instead of amines. Individual tautomers of 1,4(3,4)-DP were observed in the ^{1}H NMR spectra of one derivative depending on temperature and concentration. On the other hand, only 1,4-DP was found in the solid state by single-crystal X-ray crystallography.

1. Introduction

Dihydropyrimidine (DP) could be theoretically represented as nine isomers including tautomers when it bears different substituted groups.[1] Moreover, DPs in some cases were spontaneously oxidized during isolation or storage and decomposed under acidic conditions. Therefore, it is unstable and sometimes difficult to handle.[2] The Cho, Kappe, and Atwal groups reported the synthesis of a series of 1,4 (3,4)-dihydropyrimidines (tautomeric mixture) **A**,[2a,3c] 4,5-DP **B**,[2b] *N*-substituted 3,4-DP **C**,[2a,c] dihydropyrimidin-2-ones (thiones) **D**,[3a,b,4] *N*-substituted dihydropyrimidin-2(1*H*)-ones (thiones) **E**,[3a,b,5b] and *N*-substituted dihydropyrimidin-2(3*H*)-ones **F**[3a] (Fig. 1). The classes of the compounds **C**[5a,b] and **E**[5b,c] have received significant attention because of their pharmacological activity in the cardiovascular system.[5] Studies of DPs having the 4-phenyl group have predominated over those of 4-unsubstituted DPs owing to their synthetic accessibility[2a–c,4a,b] as well as to their pharmacological activity. During our studies of the synthesis of HCV inhibitors,[6] we sought to obtain the intermediates DPs **1** and **2**, which have a methylene group at position-4 and an amino group at position-2 (Fig. 2). Straightforward access to this class of DPs might be through the condensation of guanidine derivatives, formaldehyde, and acetoacetate. However, there is no example of this type of condensation presumably because of the difficulty in controlling the reaction with highly reactive formaldehyde or its equivalents. In addition, the difficulty may be due to the instability of the 4-unsubstituted DPs[2d,7] to oxidation. In order to obtain novel 4-unsubstituted DPs with an amino moiety, we planned to develop a method for the nucleophilic substitution of 2-methylthio DP **G**, which can be obtained from dihydropyrimidin-2-ones (thiones) **H**[3,4] (Scheme 1). We thought that it might be useful to provide a series of 2-amino-4-unsubstituted DPs **I** not only for our synthetic interest in HCV inhibitors but also for other studies of medicinal chemistry.

However, the reactivity at position-2 of dihydropyrimidines (DP) is quite different from that of pyrimidines. In fact, compared with well-known nucleophilic substitutions of pyrimidines having a leaving group at position-2,[3c,8] those of DPs are rare because of low reactivity at position-2. Actually, our theoretical study revealed that the LUMO energy level of DPs, such as 2-chlorodihydropyrimidine-5-carboxylic acid (3,4-DP **J** and 1,4-DP **K**) was higher about 11.8–17.5 kcal/mol than that of 2-chloropyrimidine-5-carboxylic

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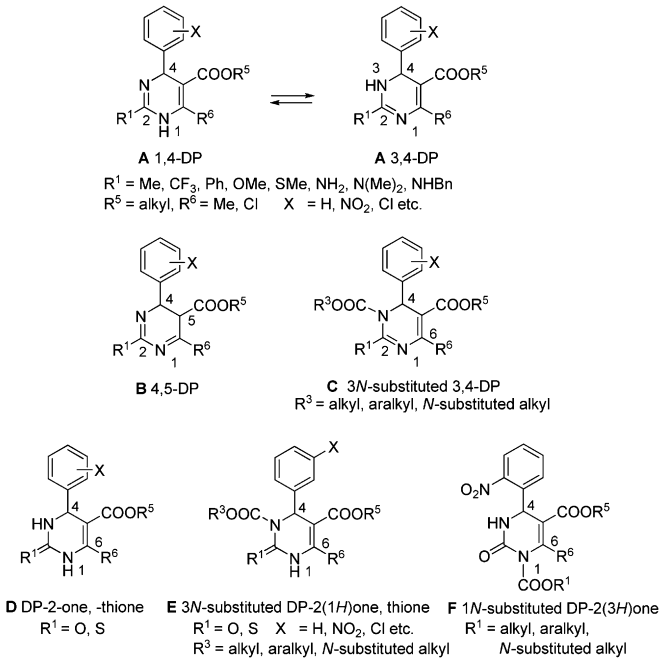


Fig. 1. A variety of dihydropyrimidines.

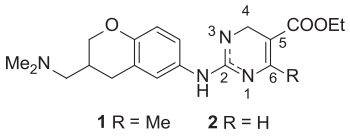
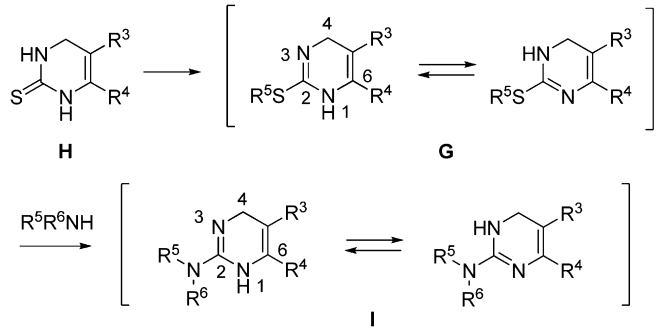


Fig. 2. Dihydropyrimidines with methylene group at position-4. (In order to simplify discussion of results, the numbering system as indicated in Figs. 1 and 2 is used throughout; but, proper nomenclature is assigned to each compound as it appears in the Experimental section.)



Scheme 1. Nucleophilic substitution at position-2 of dihydropyrimidines.

acid **L**. This high lying LUMO energy level of DPs induced a barrier for attack by the HOMO of the nucleophiles, such as aniline (Supplementary data).

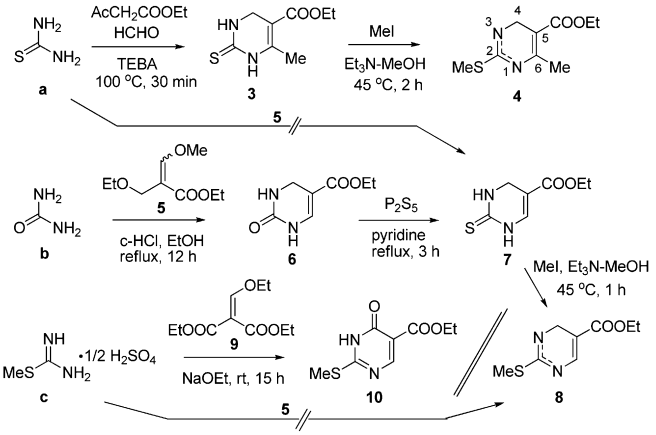
Thus, only a few reports are limited to substitution at position-2 of 4-phenyl-DPs,[1e,3b,c,9] which are more stable and easily isolated than 4-unsubstituted DP. Moreover, the yields are not always satisfactory. Namely, Atwal reported the construction of 2-amino-4-phenyl DPs by aminolysis with NH_3 or CH_3NH_2 at position-2 of 1,4 (3,4)-DPs **C** (R_1=OCH_3) in 30–54% yield (Fig. 1).[3b] Kappe obtained 2-benzylamino-1,4-DP **A** in 58% yield by the microwave irradiation of a mixture of the 2-methylthio-1,4-DP TFA salt **A** and benzylamine at 120 °C.[3c] Overman reported the synthesis of 2-amino-DP **A** in 77% yield by aminolysis (NH_3/NH_4Cl, 70 °C, 12 h, in a sealed tube) with the DP having a pyrazole moiety at position-2.[9]

However, the nucleophilic substitution at position-2 of 4-unsubstituted DPs **G** was not reported. Herein, we report the synthesis of novel 4-unsubstituted DP **I** by nucleophilic substitution.

2. Results and discussion

2.1. Synthesis of 4-unsubstituted DPs 4 and 8

Initially, synthesis of 4-unsubstituted DPs **4** and **8** was carried out. Thus, compound **3** was prepared from thiourea **a**, ethyl acetoacetate, and formaldehyde in the presence of 10 mol % TEBA (benzyltriethylammonium chloride) at 100 °C for 30 min (Scheme 2).[10] The methylation of **3** with CH_3I (10 equiv) afforded DP **4** in 76% yield.



Scheme 2. Synthesis of dihydropyrimidines with a methylene group and pyrimidine with an oxo group at position-4.

Subsequently, to obtain DPs without a methyl group at position-6, the cyclization of urea **b** with ethyl 3-ethoxy-2-methoxymethylene-propionate **5**[12] was carried out to afford dihydropyrimidin-2-one **6**. Treatment of **6** with P_2S_5 furnished dihydropyrimidin-2-thione **7** in 57% yield. On the other hand, the direct synthesis of **7** from thiourea **a** and **5** gave a complex mixture. The methylation of **7** was performed with 10 equiv of CH_3I in Et_3N/CH_3OH at 45 °C for 1 h to afford DP **8**. However, the cyclization of 2-methyl-2-thiopseudourea sulfate **c** with **5** under similar conditions did not give **8**, because compound **8** was very unstable to oxygen and easily decomposed. Therefore, compound **8** was immediately subjected to next reaction.

The cyclization of 2-methyl-2-thiopseudourea sulfate **c** and **9**[13] provided pyrimidine **10**[8a] with an oxo group at position-4 in the presence of NaOEt/EtOH at room temperature for 15 h in 81% yield.

2.2. Tautomerism of DP 4

Generally, individual tautomers of heterocycles are not observed at room temperature in ^1H NMR spectra, but a mixture of two individual tautomers in ^1H NMR ($CDCl_3$ and DMSO-d_6) was observed in the case of DP **4** (Fig. 3). In each solvent, the signals of NH protons (δ 9.24, 8.19 in DMSO-d_6, δ 5.89, 5.16 in $CDCl_3$) and two methylene protons (δ 4.10, 3.92 in DMSO-d_6, δ 4.29, 4.12 in $CDCl_3$) indicated that the two isomers were the 1,4- and 3,4-dihydroisomers, and other isomers were ruled out. The major isomer was assigned to the 1,4-dihydroisomer by HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) experiments (Supplementary data). The ratio of

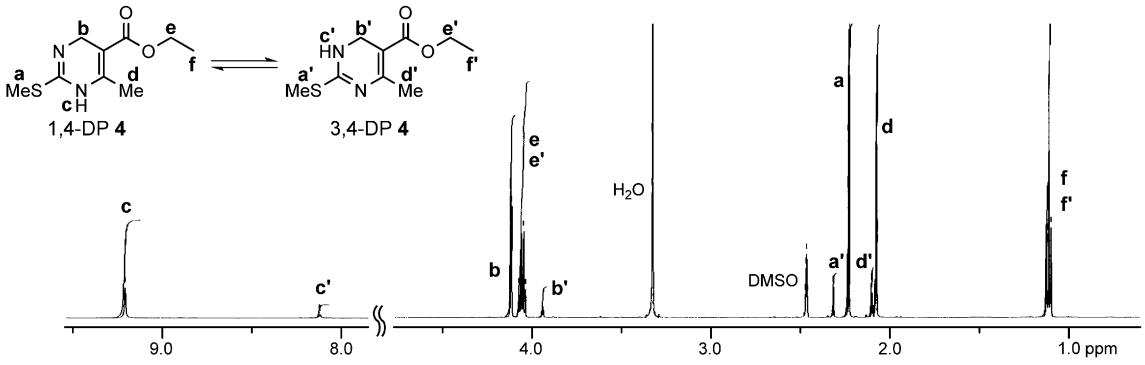


Fig. 3. ^{1}H NMR of the tautomeric mixture of DP **4** (0.100 M, 25 °C) in DMSO-d_6.

1,4-DP (major) and 3,4-DP (minor) tautomers of **4** changed in $CDCl_3$ and DMSO-d_6 depending on temperature or concentration (Tables 1 and 2). Thus, the 1,4-DP major isomer gradually decreased in amount and was converted into the 3,4-DP isomer at elevated temperatures or high concentrations. When a 0.012 M solution of DP **4** in $CDCl_3$ was heated from 5 °C to 55 °C, the ratio of 1,4-/3,4-DP changed from 5.9 to 3.5. Similarly, the ratio of 1,4-/3,4-DP changed from 7.5 to 4.2 in DMSO-d_6 (0.050 M) when the temperature was changed from 15 °C to 85 °C. At the same temperature (25 °C), the ratio of 1,4-/3,4-DP (4.7) was observed from 0.012 M to 0.025 M in $CDCl_3$ but not in 0.050 M (average spectrum), or the ratio of 1,4-/3,4-DP (from 7.0 to 6.5) was observed from 0.012 M to 0.100 M in DMSO-d_6. Interestingly, the single-crystal X-ray crystallographic analysis of DP **4** revealed only the 1,4-DP form, because of its double-bond character: (i) *C*(2)–*N*(3) (1.263(3) (Å)) (ii) *C*(2)–*N*(1) (1.382(3) (Å)) (iii) *N*(1)–*C*(2) (1.386(3) (Å)) (Fig. 4).[11] Therefore, when a crystal (1,4-form) was dissolved in each solvent, tautomerism was initiated and the solution became a mixture of 1,4-DP and 3,4-DP.

Table 1
Tautomerization of **4** in ^{1}H NMR in $CDCl_3$

Concentration (M)	Temperature (°C)	Ratio of 1,4-/3,4-DP **4**
0.012	25	4.7
0.025	25	4.7
0.050	25	Average spectrum
0.100	25	Average spectrum
0.012	5	5.9
0.012	15	5.3
0.012	35	4.6
0.012	45	4.3
0.012	55	3.5

Table 2
Tautomerization of **4** in ^{1}H NMR in DMSO-d_6

Concentration (M)	Temperature (°C)	Ratio of 1,4-/3,4-DP **4**
0.012	25	7.0
0.025	25	6.8
0.050	25	6.6
0.100	25	6.5
0.050	15	7.5
0.050	35	6.1
0.050	45	5.9
0.050	55	5.4
0.050	65	4.7
0.050	75	4.4
0.050	85	4.2
0.050	95	Average spectrum

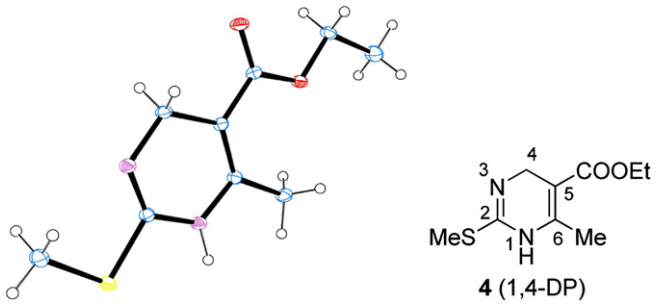
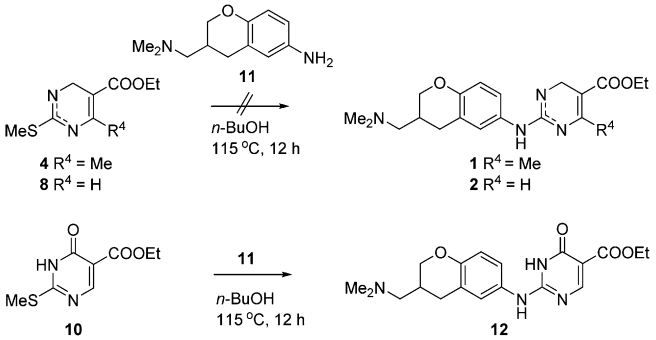


Fig. 4. ORTEP drawing of 1,4-DP **4**.

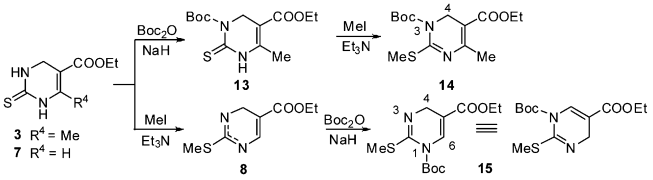
2.3. Regioselective alkoxycarbonylation at position-3 or position-1

The nucleophilic substitution of amine **11** to DPs **4**, **8**, and pyrimidine **10** was investigated (Scheme 3). When both DPs **4** and **8** were treated with aromatic amine **11** in *n*-BuOH at 115 °C for 12 h, neither of the desired compounds **1** and **2** was obtained and a complex mixture resulted. On the other hand, the reaction of **11** with pyrimidine **10** furnished 2-amino DP **12** in 67% yield. The successful result of the reaction from **10** and **11** led us to the assumption that the oxo group at position-4 together with the ester group activated position-2 through the conjugate double bond system of **10**. Therefore, alkoxycarbonylation of an electron-withdrawing group (a Boc group) at position-3 of DPs was carried out, considering that introduction of this group to **4** or **8** may enhance the activity of position-2 through a conjugated double bond system by an electron-withdrawing ester group at position-5. Thus, the reaction of the sodium salt of compound **3** in DMF with 2 equiv of



Scheme 3. Nucleophilic substitution of amine **11** to dihydropyrimidines **4**, **8**, and pyrimidine **10**.

di-*tert*-butyl dicarbonate (Boc_2O) occurred regioselectively to give 3-*N*-substituted DP **13** in 90% yield (Scheme 4).[2a,3b] The regioselectivity of Boc protection was confirmed by three-bond long-range coupling (HMBC) between methylene protons at position-4 and the carbonyl carbon of the Boc group (Supplementary data). The selectivity of **3** to **13** may be due to more steric hindrance around position-1 because of the methyl group of **3**. The successive methylation of **13** was carried out with 10 equiv of CH_3I in Et_3N/CH_3OH at 45 °C for 1 h to afford 3,4-DP **14** in 87% yield. The protection of **7** under the same reaction conditions gave no protected compound corresponding to **13** but yielded a mixture. Therefore, DP **7** was initially converted to **8** by methylation, followed by protection to selectively furnish a single compound **15** in 44% yield (two steps). The position of the Boc group was determined to be position-1 by an NOE experiment (Supplementary data). Thus, when the *t*-Bu group (δ=1.57, in $CDCl_3$) of **15** was irradiated, an NOE enhancement (1.4%) at H-6 (δ=7.78) was observed, indicating position-1 of the Boc group. On the other hand, when the *t*-Bu group (δ=1.53) of **14** was irradiated, a positive NOE (1.5%) was observed at H-4 (δ=4.34).



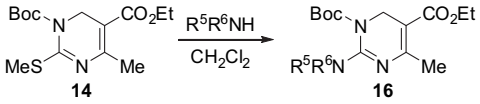
Scheme 4. Preparation of dihydropyrimidin-2-thione, 3,4- and 1,4-dihydropyrimidine derivatives.

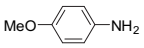
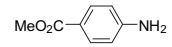
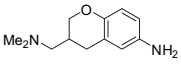
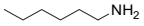
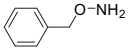
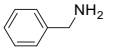
2.4. Substitution of 4-unsubstituted DP with amines or phenylhydrazine

Subsequently, the nucleophilic substitution of a wide variety of aromatic and aliphatic amines was investigated (Table 3).

Initially, the substitution of **14** with **11** was carried out under the same reaction conditions as those of Scheme 3. However, *N*-Boc compound of **1** was not obtained, but a complex mixture resulted. Therefore, milder reaction conditions were examined. Thus, a mixture of DP **14** and 3 equiv of aniline in CH_2Cl_2 was heated at reflux to provide DP **16a** in 97% yield after 24 h (entry 1). It was found that the addition of 0.1 equiv of pyridinium *p*-toluenesulfonate (PPTS) resulted in the completion of the reaction within 6.5 h at room temperature, but in a slightly lower isolated yield (entry 2). The faster completion may be due to activation by the protonation on the carbonyl group of the ester or the N-1 atom of DP. Since aromatic amines showed higher reactivity, conditions without PPTS were evaluated (entries 3–5). Also, the electronic effect of functional groups on the aromatic ring was examined using aniline derivatives with an electron-donating group, OMe or an electron-withdrawing group, COOMe. The compounds **16b** and **16c** were obtained in more than 90% yield without finding any effect by different functional groups at position-4. Different from the result of substitution of **4** with **11**, desired DP **16d** was obtained from the reaction of Boc-protected compound **14** with **11** in 84% yield under the reaction conditions (entry 5). In the case of aliphatic amines, it was better to add PPTS to complete the reaction in a reasonable period (entries 6–8). But secondary amines were found to react very slowly under these conditions. For example, Et_2NH and piperazine gave no adduct with the recovery of the starting material. Only a less hindered pyrrolidine could attack the C-2 position to furnish compound **16h** in moderate yield (entry 9).

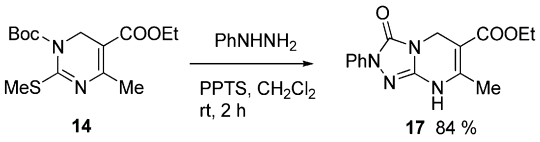
Table 3
Nucleophilic substitution of amines to dihydropyrimidine **14**



Entry	R^5R^6NH	Temp	Time (h)	Product	Yield (%)
1		Reflux	24	**16a**	97
2[a]		rt	6.5	**16a**	89
3		Reflux	24	**16b**	91
4		Reflux	24	**16c**	92
5		Reflux	24	**16d**	84
6[a]		Reflux	24	**16e**	90
7[a]		rt	1	**16f**	91
8[a]		Reflux	24	**16g**	76
9[a]		Reflux	24	**16h**	44

[a] With 0.1 equiv of PPTS.

An exceptional result was obtained in the reaction of phenylhydrazine (0.1 equiv of PPTS, room temperature, 2 h) (Scheme 5). The generation of bicyclic DP **17** lacking the *t*-Boc group was suggested by ^1H NMR and mass spectra. The phenyl group was presumed to be at position-2 of the bicyclic DP, on the basis of the reaction mechanism: the primary nitrogen initially attacked the carbon at position-2 of DP, and then the secondary nitrogen reacted with the carbonyl carbon of the *t*-Boc group to construct the 3-oxo-2-phenyl-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrimidine skeleton. The chemical structure of **17** was confirmed by X-ray crystallographic analysis (Fig. 5 and Supplementary data).[11]



Scheme 5. Bicyclic dihydropyrimidine **17**.

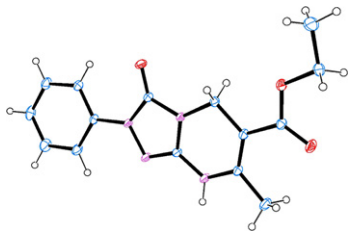
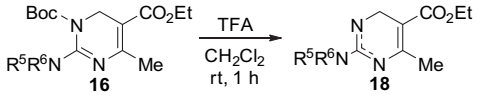
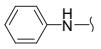
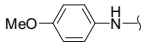
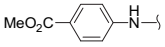
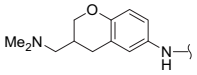
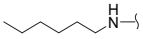
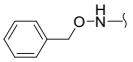
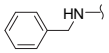


Fig. 5. ORTEP drawing of 1,4-DP **17** with 30% thermal ellipsoid probability.

1,4(3,4)-DPs **18** without any substitution at position-4 were isolated after the deprotection of **16** with trifluoroacetic acid (TFA) at room temperature, as shown in Table 4. Thus, compound **1**[14] was obtained from **3** in excellent yield as a stable powder. Regarding the

Table 4
Deprotection of **16** with TFA



Entry	R^5R^6N—	Product	Yield (%)
1		**18a**	quant.
2		**18b**	quant.
3		**18c**	96
4		**1**	quant.
5		**18e**	84
6		**18f**	84
7		**18g**	94
8		**18h**	78

stability of DPs **18**, compounds **18e** with an alkyl amino residue and **18f** with a benzyloxyamino residue were so unstable as to be partially oxidized to pyrimidine derivatives during SiO_2 column chromatography or even on standing at room temperature.

On the other hand, the nucleophilic substitution of 6-unsubstituted compound **15** with aniline or 4-methoxyaniline gave no substituted DP under the same reaction conditions for that of **14** with the amines.

Consequently, for nucleophilic substitution at position-2 of dihydropyrimidines and pyrimidine, we obtained different results for reactions from **4** to **1** and from **10** to **12** (Scheme 3), and comparative results for reactions from **4** to **1** and from **14** to **16d** (Scheme 3 and Table 3). In the case of DP having an electron-withdrawing group (a Boc group) at position-3, the reactivity at position-2 of a DP ring was enhanced through a conjugated double bond system by the ester group at position-5 to afford DPs **16**. However, lower reactivity in the case of DP **4** without the Boc group and in DP **15** with a non-conjugated double bond did not give the desired DPs. On the other hand, the reaction of pyrimidine **10** with **11** easily occurred because the oxo group at position-4 together with the ester group activated position-2 through the conjugate double bond system of **10**. Thus, the different reactivities of these compounds may be due to substitution at positions-1, 3, or 4 of the DP skeleton.

3. Conclusions

Novel dihydropyrimidines **14** without any substituted group at position-4 were synthesized via compound **3** in good yields. Subsequently, a variety of nucleophilic substitutions at position-2 of a DP skeleton were carried out to provide DP **16** with various amino moieties in good to excellent yields. The successive deprotection of the Boc group furnished a variety of novel DPs **1** and **18**. Moreover, novel bicyclic DP **17** was obtained by employing phenylhydrazine instead of amines. Different reactivity between a protected DP with a Boc group and a non-protected DP was observed in **4** and **14**, as well as between protected DPs **14** and **15**. Interestingly, individual tautomers of 1,4 (3,4)-DP were observed in the ^1H NMR spectra of DP **4** depending on temperature and concentration. On the other hand, only 1,4-DP was found in the solid state by single-crystal X-ray crystallography.

The synthetic methods and compounds described herein will likely find use in the field of fine chemistry and medicinal chemistry.

4. Experimental section

4.1. General

Unless otherwise noted, reactions were performed under argon. Melting points were determined on Yanaco micro melting point apparatus and uncorrected. IR spectra were measured on SHIMADZU FTIR-8300 spectrometer. ^1H 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) 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) 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. Elemental analyses were performed by Yanaco CHN CORDER MT-6. Flash column chromatography was performed on silica gel 60 N (Kanto, 40–60 mm) using indicated solvent. Reactions and fractions of chromatography were monitored by employing pre-coated silica gel 60 F_{254} plates (Merck).

*4.1.1. Ethyl 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3**)[10].* A mixture of thiourea (5.71 g, 75.0 mmol), 37% formaldehyde solution (50.5 mmol, 4.10 mL), ethyl acetoacetate (6.51 g, 50.0 mmol), and benzyltriethylammonium chloride (1.14 g, 5.00 mmol) was heated at 100 °C for 30 min, and the formed precipitate was corrected by filtration. The filtrate was washed with water and ether, and dried in vacuo to provide the compound **3** (1.45 g, 15%). ^1H NMR and IR spectra were identical to those reported previously.

*4.1.2. Ethyl 6-methyl-2-methylsulfanyl-1,4-dihydropyrimidine-5-carboxylate and ethyl 4-methyl-2-methylsulfanyl-1,6-dihydropyrimidine-5-carboxylate (**4**).* To a solution of the compound **3** (530 mg, 2.65 mmol) and triethylamine (3.80 mL, 27.3 mmol) in MeOH (10 mL) was added iodomethane (1.70 mL, 27.3 mmol) at 0 °C. The mixture was stirred for 2 h at 45 °C, and water was added. The organic materials were extracted with EtOAc, and the combined organic extracts were washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc=3:1) to give the dihydropyrimidine **4** [430 mg, 76%, a mixture of 1,4- and 1,6-dihydro tautomers (6.6:1)] as colorless crystals. Mp 113–115 °C (*n*-hexane–$CHCl_3$). IR (KBr) 3318, 1668, 1647, 1497, 1171 cm^{-1}. δ_H (600 MHz, DMSO-d_6, 25 °C, 0.1 M) 1.17 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.11 (2.61H, s, C6–CH_3), 2.13 (0.39H, s, C4–CH_3), 2.26 (2.61H, s, SCH_3), 2.34 (0.39H, s, SCH_3), 3.92 (0.26H, s, C6–H_2), 4.04 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.10 (1.74H, s, C4–H_2), 8.19 (0.13H, s, N*H*), 9.25 (0.87H, s, N*H*). δ_C (150 MHz, DMSO-d_6) 12.7, 14.5, 17.4, 46.6, 59.2, 94.0, 147.8, 151.5, 166.2. LRMS (EI) *m*/*z* 214 (M^+). HRMS (EI): M^+, found 214.0770. $C_9H_{14}N_2O_2S$ requires 214.0776. The each tautomer of **4** in ^1H NMR was assigned by HSQC and HMBC experiments.

*4.1.3. Ethyl 2-ethoxymethyl-3-methoxy-acrylate (**5**)[12].* To a suspension of sodium ethoxide (9.12 g, 134 mmol) in dry toluene (100 mL) was added a solution of ethyl formate (9.93 g, 134 mmol) and ethyl 3-ethoxypropionate (9.79 g, 67.0 mmol) in dry toluene (40 mL) at 0 °C. After stirring at 0 °C for 2 h, dimethylsulfate (12.8 mL, 135 mmol) was added. The reaction mixture was stirred at 50 °C for 12 h. The mixture was washed with aqueous 2 M NaOH, 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=20:1 to 1:2) to give the compound **5** (6.54 g, 52%) as a mixture of isomers.

*4.1.4. Ethyl 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**6**)*[10]. A mixture of the compound **5** (6.54 g, 34.0 mmol), urea (2.04g, 34.0 mmol), and concentrated HCl (2.5 mL) in ethanol (115 mL) was heated at reflux for 12 h. After concentrated under reduced pressure, the residue was recrystallized from ethanol to give **6** (1.78 g, 31%) as colorless prisms. Mp 183–185 °C. IR (KBr) 3251, 1720, 1703, 1268 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, CH_2CH_3), 4.19 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.20 (2H, s, C4–H_2), 5.10–5.35 (1H, br s, N*H*), 7.10–7.45 (1H, br s, N*H*), 7.21 (1H, d, *J* 5.4 Hz, C6–*H*). δ_C (150 MHz, DMSO-d_6) 14.3, 40.1, 59.5, 98.7, 137.0, 152.2, 165.0. LRMS (EI) *m*/*z* 170 (M^+). HRMS (EI): M^+, found 170.0694. $C_7H_{10}N_2O_3$ requires 170.0691.

*4.1.5. Ethyl 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7**)*[15]. Phosphorous pentasulfide (1.72 g, 7.74 mmol) was added to a solution of the compound **6** (1.72 g, 10.1 mmol) in pyridine (17 mL), and the mixture was heated at reflux for 3 h. After concentrated in vacuo, the residue was treated with H_2O and cold ethanol to give a crude solid, which recrystallized from ethanol to give **7** (1.14 g, 60%) as a pale yellow powder. IR (KBr) 3279, 1698, 1657, 1580, 1183 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, CH_2CH_3), 4.19 (2H, t, *J* 1.2 Hz, C4–H_2), 4.21 (2H, q, *J* 7.2 Hz, CH_2CH_3), 6.55–6.70 (1H, br s, N*H*), 7.07 (1H, dt, *J* 5.4, 1.2 Hz, C6–*H*), 7.45–7.62 (1H, br s, N*H*). δ_C (150 MHz, DMSO-d_6) 14.4, 40.4, 60.1, 100.6, 133.4, 164.8, 175.7. LRMS (EI) *m*/*z* 186 (M^+). HRMS (EI): M^+, found 186.0462. $C_7H_{10}N_2O_2S$ requires 186.0463.

*4.1.6. Ethyl 2-methylsulfanyl-6-oxypyrimidine-5-carboxylate (**10**).* To a solution of sodium ethoxide (1.36 g, 20.0 mmol) in ethanol (15 mL) was added *S*-methylisothiourea sulfate (5.57 g, 40.0 mmol) at 0 °C. After a few minutes, diethyl ethoxymethylenemalonate (4.00 mL, 19.8 mmol) was added. After stirring at 0 °C for 3 h, a solution of sodium ethoxide (1.36 g, 20.0 mmol) in ethanol (15 mL) was added. The resulted solution was stirred at room temperature overnight. Ethanol was removed under reduced pressure and the pale yellow residue was dissolved in water. After filtration, the aqueous filtrate was washed with ether and acidified with acetic acid (10 mL). The organic materials were extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Recrystallization of the residue with $CHCl_3$ gave compound **10** (3.44 g, 81%) as colorless needles. Mp 129–130 °C ($CHCl_3$), lit.[16] 132–133 °C (benzene/petroleum ether). IR (KBr) 3435, 2902, 2805, 1739, 1701, 1529, 1170 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.42 (3H, t, *J* 6.8 Hz, CH_2CH_3), 2.60 (3H, s, SCH_3), 4.43 (2H, q, *J* 6.8 Hz, CH_2CH_3), 8.75 (1H, s, C4–*H*). δ_C (150 MHz, DMSO-d_6) 13.0, 14.1, 60.2, 111.7, 157.8, 158.9, 163.6, 168.0. LRMS (EI) *m*/*z* 214 (M^+). HRMS (EI): M^+, found 214.0458. $C_8H_{10}N_2O_3S$ requires 214.0412.

*4.1.7. Ethyl 2-(3-dimethylaminomethyl-chroman-6-ylamino)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**12**).* A mixture of amine **11** (200 mg, 0.971 mmol) and dihydropyrimidine **10** (249 mg, 1.16 mmol) in *n*-butanol (3 mL) was heated at 115 °C for 12 h. After the solvent was removed under reduced pressure, the residue was recrystallized from DMF to give **12** (242 mg, 67%) as a colorless powder. IR (KBr) 1697, 1650, 1498, 1297 cm^{-1}. δ_H (600 MHz, DMSO-d_6) 1.24 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.13–2.38 (3H, m, ArCH_2CH), 2.25 (6H, s, NMe_2), 2.46 (1H, dd, *J* 16.2, 7.8 Hz, $Me_2NCH_aH_b$), 2.79 (1H, dd, *J* 16.2, 5.4 Hz, $Me_2NCH_aH_b$), 3.77 (1H, dd, *J* 10.8, 7.8 Hz, OCH_aH_b), 4.12 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.16–4.20 (1H, m, OCH_aH_b), 6.70 (1H, d, *J* 8.4 Hz, Ar–*H*), 7.26 (1H, d, *J* 8.4 Hz, Ar–*H*), 7.27 (1H, s, Ar–5-*H*), 8.40 (1H, s, C6–*H*), 9.10–10.90 (1H, br s, N*H*). δ_C (150 MHz, $CDCl_3$) 14.4, 29.0, 29.8, 45.4, 59.5, 60.5, 68.5, 105.3, 116.2, 119.7, 121.4, 121.6, 123.4, 130.4, 151.2, 156.6, 162.0, 164.4. LRMS (EI) *m*/*z* 372 (M^+). HRMS (EI): M^+, found 372.1787. $C_{19}H_{24}N_4O_4$ requires 372.1798.

*4.1.8. 1-tert-Butyl 5-ethyl 4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (**13**).* To a suspension of sodium hydride (60% dispersion in mineral oil, 752 mg, 18.8 mmol) in DMF (20 mL) was added compound **3** (1.87 g, 9.34 mmol) in DMF (30 mL) at 0 °C. After stirring at 0 °C for 10 min, Boc_2O (4.10 g, 18.8 mmol) in DMF (30 mL) was added, and the mixture was stirred at room temperature for 2 h. 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=5:1) to give the compound **13** (2.52 g, 90%) as pale yellow needles. Mp 121–122 °C (*n*-hexane/EtOAc). IR (KBr) 2980, 1730, 1657, 1507, 1230 cm^{-1}. δ_H (600 MHz, DMSO-d_6) 1.21 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.46 (9H, s, CMe_3), 2.21 (3H, s, C4–CH_3), 4.11 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.23 (2H, s, C6–H_2), 11.18 (1H, s, N*H*). δ_C (100 MHz, DMSO-d_6) 14.3, 16.3, 27.6, 43.1, 60.2, 83.7, 101.9, 145.3, 152.6, 164.7, 178.2. LRMS (EI) *m*/*z* 300 (M^+). HRMS (EI): M^+, found 300.1156. $C_{13}H_{20}N_2O_4S$ requires 300.1144. The regiochemistry of the Boc group was determined by HMBC experiment.

*4.1.9. 1-tert-Butyl 5-ethyl 4-methyl-2-methylsulfanyl-1,6-dihydropyrimidine-1,5-dicarboxylate (**14**).* A mixture of the compound **13** (1.46 g, 4.86 mmol), triethylamine (6.80 mL, 48.8 mmol) in dry MeOH (20 mL) was added iodomethane (3.00 mL, 48.2 mmol) at 0 °C, and the mixture was heated at 45 °C for 1 h. 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/ether=6:1) to give the compound **14** (1.33 g, 87%) as yellow crystals. Mp 64–67 °C (*n*-hexane). IR (KBr) 2979, 1725, 1621, 1520, 1143 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.53 (9H, s, CMe_3), 2.32 (3H, s, C4–CH_3), 2.42 (3H, s, SCH_3), 4.21 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.34 (2H, s, C6–H_2). δ_C (150 MHz, $CDCl_3$) 14.3, 15.4, 21.2, 28.0, 42.5, 60.2, 84.1, 106.3, 151.5, 153.0, 159.3, 166.1. LRMS (EI) *m*/*z* 314 (M^+). HRMS (EI): M^+, found 314.1311. $C_{14}H_{22}N_2O_4S$ requires 314.1300.

*4.1.10. 1-tert-Butyl 5-ethyl 2-methylsulfanyl-1,4-dihydropyrimidine-1,5-dicarboxylate (**15**).* To a solution of compound **7** (0.770 g, 4.14 mmol) and triethylamine (11.5 mL, 81.8 mmol) in dry MeOH (50 mL) was added iodomethane (4.90 mL, 81.9 mmol) at 0 °C, and the mixture was heated at 45 °C for 1 h. After adding water, the mixture was 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=1.5:1) to give the unstable dihydropyrimidine **8** (410 mg, 50%), which was immediately subjected to the next reaction. To a suspension of sodium hydride (60% dispersion in oil, 88.0 mg, 2.20 mmol) in DMF (5 mL) was added a solution of compound **8** (220 mg, 1.10 mmol) in DMF (3 mL) at 0 °C. After stirring at 0 °C for 10 min, Boc_2O (480 mg, 2.20 mmol) in DMF (3 mL) was added, and the mixture was stirred at room temperature for 30 min. After adding water, the mixture was 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=15:1) to give the compound **15** (289 mg, 87%) as pale yellow crystals. Mp 74–76 °C (*n*-hexane). IR (KBr) 1746, 1704, 1328, 1227, 1143 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.58 (9H, s, CMe_3), 2.30 (3H, s,

SCH_3), 4.22 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.32 (2H, s, C4–H_2), 7.78 (1H, s, C6–*H*). δ_C (150 MHz, DMSO-d_6) 14.3, 15.7, 27.7, 45.4, 60.6, 85.6, 108.5, 133.4, 148.8, 149.2, 164.5. LRMS (EI) *m*/*z* 300 (M^+). HRMS (EI): M^+, found 300.1154. $C_{13}H_{20}N_2O_4S$ requires 300.1144. The position of the Boc group was determined by HMBC experiment.

4.1.11. Typical synthetic procedure of ***16****.*

*4.1.11.1. 1-tert-Butyl 5-ethyl 4-methyl-2-phenylamino-1,6-dihydropyrimidine-1,5-dicarboxylate (****16a****).* (*Method a*-1) A mixture of **13** (63.0 mg, 0.201 mmol) and aniline (54.0 μL, 0.593 mmol) in CH_2Cl_2 (2 mL) was heated at reflux for 24 h under Ar. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/Et_2O=5:1) to give compound **16a** (70.0 mg, 97%) as pale yellow needles.

(*Method b*-1) To a stirred mixture of **14** (31.5 mg, 0.100 mmol) and aniline (27.5 μM, 0.302 mmol) in CH_2Cl_2 (1.5 mL) was added pyridinium *p*-toluenesulfonate PPTS (2.5 mg, 0.010 mmol) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred at room temperature for 6 h, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue. Compound **16a** (31.9 mg, 89%) was obtained after purification as mentioned above. Mp 118–119 °C (*n*-hexane). IR (KBr) 2979, 2929, 1699, 1604, 1552, 1143 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.53 (9H, s, CMe_3), 2.35 (3H, s, C4–CH_3), 4.21 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.47 (2H, s, C6–H_2), 7.09 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.32 (2H, t, *J* 7.2 Hz, Ar–*m*-*H*), 7.65 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 22.2, 27.9, 43.0, 59.6, 84.2, 101.7, 120.9, 123.7, 128.6, 138.3, 146.3, 153.4, 156.3, 166.2. LRMS (EI) *m*/*z* 359 (M^+). HRMS (EI): M^+, found 359.1827. $C_{19}H_{25}N_3O_4$ requires 359.1845.

*4.1.11.2. 1-tert-Butyl 5-ethyl 2-(4-methoxyphenylamino)-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16b****).* Pale yellow needles. Mp 119–121 °C (*n*-hexane). IR (KBr) 2979, 1697, 1617, 1558, 1509 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.55 (9H, s, CMe_3), 2.32 (3H, s, C4–CH_3), 3.80 (3H, s, OCH_3), 4.20 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.46 (2H, s, C6–H_2), 6.86 (2H, d, *J* 9.0 Hz, Ar–*H*), 7.56 (2H, d, *J* 9.0 Hz, Ar–*H*), 9.60–10.30 (1H, br s, N*H*). δ_C (150 MHz, $CDCl_3$) 14.4, 22.2, 28.0, 29.6, 43.0, 55.4, 59.6, 84.2, 101.3, 113.9, 122.7, 131.5, 146.8, 153.4, 156.1, 166.2. LRMS (EI) *m*/*z* 389 (M^+). HRMS (EI): M^+, found 389.1966. $C_{20}H_{27}N_3O_5$ requires 389.1951.

*4.1.11.3. 1-tert-Butyl 5-ethyl 2-(4-methoxycarbonylphenylamino)-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16c****).* Pale yellow needles. Mp 186–188 °C (*n*-hexane–$CHCl_3$). IR (KBr) 2985, 1703, 1638, 1549, 1274 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.57 (9H, s, CMe_3), 2.36 (3H, s, C4–CH_3), 3.90 (3H, s, OCH_3), 4.20 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.47 (2H, s, C6–H_2), 7.70–7.85 (2H, m, Ar–*H*), 8.00 (2H, d, *J* 8.4 Hz, Ar–*H*), 10.15–10.50 (1H, br s, N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 22.1, 27.9, 43.0, 51.9, 59.8, 84.6, 102.5, 119.9, 124.7, 130.5, 142.8, 145.8, 153.4, 155.3, 166.0, 166.7. LRMS (EI) *m*/*z* 417 (M^+). HRMS (EI): M^+, found 417.1909. $C_{21}H_{27}N_3O_6$ requires 417.1900.

*4.1.11.4. 1-tert-Butyl 5-ethyl 2-(3-dimethylaminomethyl-chroman-6-yl-amino)-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16d****).* Pale yellow powder. IR (KBr) 2978, 1698, 1555, 1500, 1217 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.54 (9H, s, CMe_3), 2.20–2.36 (3H, m, ArCH_2C*H*), 2.26 (6H, s, NMe_2), 2.31 (3H, s, C4–CH_3), 2.52 (1H, dd, *J* 7.2, 16.2 Hz, $Me_2NCH_aH_b$), 2.87 (1H, dd, *J* 4.2, 16.2 Hz, $Me_2NCH_aH_b$), 3.82 (1H, dd, *J* 7.2, 10.2 Hz, OCH_aH_b), 4.20 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.24–4.30 (1H, m, OCH_aH_b), 4.45 (2H, s, C6–H_2), 6.76 (1H, d, *J* 9.0 Hz, Ar–*H*), 7.29 (1H, d, *J* 9.0 Hz, Ar–*H*), 7.40 (1H, s, Ar–5-*H*). δ_C (150 MHz, $CDCl_3$) 14.4, 22.3, 28.0, 29.8, 30.4, 43.0, 45.8, 60.0, 61.4, 69.1, 84.1, 101.0, 116.4, 121.0, 121.3, 122.8, 130.9, 146.7, 151.2, 153.5, 156.8, 166.3. LRMS (EI) *m*/*z* 472 (M^+). HRMS (EI): M^+, found 472.2683. $C_{25}H_{36}N_4O_5$ requires 472.2686.

*4.1.11.5. 1-tert-Butyl 5-ethyl 2-hexylamino-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16e****).* Colorless oil. IR (neat) 3339, 2930, 2858, 1699, 1612, 1568, 1303, 1142 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2 Hz, NHCH$_2$CH$_2$CH$_2$CH$_2$CH_3), 1.27–1.40 (6H, m, NHCH$_2$CH$_2$CH_2CH$_2$CH_2CH$_3$), 1.29 (3H, t, *J* 7.2 Hz, OCH$_2$CH_3), 1.53 (9H, s, CMe_3), 1.55–1.65 (2H, m, NHCH$_2$CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 2.29 (3H, s, C4–CH_3), 3.40 (2H, dt, *J* 4.8, 7.2 Hz, NHCH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 4.17 (2H, q, *J* 7.2 Hz, OCH_2CH$_3$), 4.37 (2H, s, C6–H_2), 7.85–8.20 (1H, br s, N*H*). δ_C (100 MHz, $CDCl_3$) 14.0, 14.4, 22.5, 22.8, 26.6, 27.9, 28.9, 31.4, 41.6, 43.1, 59.3, 83.6, 99.1, 150.1, 153.6, 158.0, 166.6. LRMS (EI) *m*/*z* 367 (M^+). HRMS (EI): M^+, found 367.2462. $C_{19}H_{33}N_3O_4$ requires 367.2471.

*4.1.11.6. 1-tert-Butyl 5-ethyl 2-benzyloxyamino-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16f****).* Colorless oil. IR (NaCl) 3294, 2983, 1706, 1631, 1367, 1228, 1070 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.46 (9H, s, CMe_3), 2.29 (3H, s, C4–CH_3), 4.17 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.37 (2H, s, C6–H_2), 5.06 (2H, s, CH_2Ph), 7.05 (1H, s, N*H*), 7.31–7.42 (5H, m, Ar–*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 18.3, 28.0, 41.6, 59.9, 76.4, 82.3, 100.5, 128.1, 128.4, 128.6, 137.2, 142.6, 145.0, 151.8, 165.5. LRMS (EI) *m*/*z* 389 (M^+). HRMS (EI): M^+, found 389.1936. $C_{20}H_{27}N_3O_5$ requires 389.1951.

*4.1.11.7. 1-tert-Butyl 5-ethyl 2-benzylamino-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16g****).* Colorless crystals. Mp 72–73 °C (EtOAc). IR (KBr) 3330, 2975, 1714, 1691, 1558, 1300, 1153, 1115 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.50 (9H, s, CMe_3), 2.30 (3H, s, C4–CH_3), 4.18 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.39 (2H, s, C6–H_2), 4.62 (2H, s, CH_2Ph), 7.27–7.38 (5H, m, Ar–*H*), 8.32 (1H, br s, N*H*). δ_C (100 MHz, $CDCl_3$) 14.4, 22.7, 28.0, 43.3, 45.6, 59.5, 83.9, 97.7, 127.4, 128.0, 128.6, 138.3, 150.0, 153.5, 157.7, 166.6. LRMS (EI) *m*/*z* 373 (M^+). HRMS (EI): M^+, found 373.1985. $C_{20}H_{27}N_3O_4$ requires 373.2002.

*4.1.11.8. 1-tert-Butyl 5-ethyl 2-pyrrolidyl-4-methyl-1,6-dihydropyrimidine-1,5-dicarboxylate (****16h****).* Colorless oil. IR (NaCl) 2977, 1720, 1556, 1371, 1298, 1273 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.47 (9H, s, CMe_3), 1.94 (4H, s, NCH$_2$CH_2CH_2CH$_2$), 2.34 (3H, s, C4–CH_3), 3.46 (2H, br s, NCH_2CH$_2$), 3.62 (2H, br s, NCH_2CH$_2$), 4.18 (2H, d, *J* 7.2 Hz, CH_2CH$_3$), 4.78 (2H, br s, C6–H_2). δ_C (100 MHz, $CDCl_3$) 14.5, 22.1, 24.7, 25.6, 28.1, 43.0, 47.8, 59.3, 82.2, 103.7, 149.3, 151.8, 159.0, 166.5. LRMS (EI) *m*/*z* 337 (M^+). HRMS (EI): M^+, found 337.1999. $C_{17}H_{27}N_3O_4$ requires 337.2002.

*4.1.11.9. Ethyl 7-methyl-3-oxo-2-phenyl-2,3,5,8-tetrahydro[1,2,4]-triazol [4,3-a]pyrimidine-6-carboxylate (****17****).* To a stirred solution of **14** (31.4 mg, 0.100 mmol) in CH_2Cl_2 (0.5 mL) were added PPTS (2.5 mg, 0.010 mmol) in CH_2Cl_2 (1.0 mL) and phenylhydrazine (30 μM, 0.31 mmol). The mixture was stirred at room temperature for 2 h, and the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to leave the residue, which was purified with silica gel column chromatography (toluene/EtOAc=94:6) to yield compound **17** (25.2 mg, 84%) as colorless crystals. Mp 237–238 °C (EtOAc). IR (KBr) 3228, 3112, 1704, 1660, 1621, 1263, 1076 cm^{-1}. δ_H (400 MHz, DMSO-d_6) 1.21 (3H, t, *J* 7.2 Hz, CH$_2$CH_3), 2.29 (3H, s, C7–CH_3), 4.09 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 4.28 (2H, s, C5–H_2), 7.14 (1H, t, *J* 8.0 Hz, Ar–*p*-*H*), 7.41 (2H, t, *J* 8.0 Hz, Ar–*m*-*H*), 7.81 (2H, d, *J* 8.0 Hz, Ar–*o*-*H*), 10.38 (1H, br s, N*H*). δ_C (100 MHz, DMSO-d_6) 14.4, 18.3, 39.0, 59.6, 91.7, 117.2, 124.3, 129.2, 138.1, 140.8, 146.4, 149.5, 165.2. LRMS (EI) *m*/*z* 300 (M^+). HRMS (EI): M^+, found 300.1214. $C_{15}H_{16}N_4O_3$ requires 300.1222.

4.1.12. Typical synthetic procedure of ***18***

*4.1.12.1. Ethyl 2-phenylamino-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18a**).* To a stirred solution of **16a** (27.4 mg, 0.0763 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.50 mL, 6.7 mmol) at 0 °C. Stirring was continued at room temperature for 1 h, and the reaction mixture was basified with 0.5 M aqueous NaOH. The mixture was extracted with EtOAc, and the combined organic extracts were washed with 0.5 M aqueous NaOH and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained colorless powder was recrystallized from MeOH to give quantitatively compound **18a** (19.6 mg) as colorless crystals. Mp 171–173 °C ($CHCl_3$). IR (KBr) 3370, 3180, 3056, 2975, 2844, 1681, 1648, 1628, 1265, 1097 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.18 (3H, s, C4–CH_3), 3.98 (2H, s, C6–CH_2), 4.14 (2H, q, *J* 7.2 Hz, CH_2CH_3), 6.97 (2H, d, *J* 7.6 Hz, Ar–*o*-*H*), 7.08 (1H, t, *J* 7.6 Hz, Ar–*p*-*H*), 7.34 (2H, t, *J* 7.6 Hz, Ar–*m*-*H*). δ_C (100 MHz, $CDCl_3$) 14.4, 18.5, 40.3, 59.6, 95.6, 123.6, 123.9, 129.7, 146.2, 147.89, 147.94, 166.0. LRMS (EI) *m*/*z* 259 (M^+). HRMS (EI): M^+, found 259.1303. $C_{14}H_{17}N_3O_2$ requires 259.1321.

*4.1.12.2. Ethyl 2-(4-methoxyphenylamino)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18b**).* Colorless powder. IR (KBr) 1709, 1687, 1666, 1515, 1203 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.44 (3H, s, CH_2CH_3), 3.83 (3H, s, OCH_3), 4.16 (2H, s, C6–H_2), 4.21 (2H, q, *J* 7.2 Hz, CH_2CH_3), 6.97 (2H, d, *J* 9.0 Hz, Ar–*H*), 7.18 (2H, d, *J* 9.0 Hz, Ar–*H*). δ_C (150 MHz, $CDCl_3$) 14.2, 17.5, 39.9, 55.6, 60.6, 115.5, 125.2, 127.3, 151.4, 159.7, 163.7, 164.0, 164.6. LRMS (FAB) *m*/*z* 290 (MH^+). HRMS (FAB): MH^+, found 290.1523. $C_{15}H_{20}N_3O_3$ requires 290.1505.

*4.1.12.3. Ethyl 2-(4-methoxycarbonylphenylamino)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18c**).* Colorless needles. Mp 199–200 °C (*n*-hexane/$CHCl_3$). IR (KBr) 1689, 1633, 1594, 1252 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.32 (3H, s, C4–CH_3), 3.91 (3H, s, OCH_3), 4.09 (2H, s, C6–H_2), 4.19 (2H, q, *J* 7.2 Hz, CH_2CH_3), 7.09 (2H, d, *J* 8.4 Hz, Ar–*H*), 8.04 (2H, d, *J* 8.4 Hz, Ar–*H*). δ_C (150 MHz, $CDCl_3$) 14.3, 18.2, 40.3, 52.1, 60.1, 97.2, 123.6, 126.1, 131.4, 146.4, 147.7, 148.3, 165.4, 166.6. LRMS (FAB) *m*/*z* 318 (MH^+). HRMS (FAB): MH^+, found 318.1483. $C_{16}H_{20}N_3O_4$ requires 318.1454.

*4.1.12.4. Ethyl 2-(3-dimethylaminomethyl-chroman-6-ylamino)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**1**).* Colorless powder. IR (KBr) 1677, 1631, 1492, 1263, 1099 cm^{-1}. δ_H (600 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.17–2.30 (3H, m, $ArCH_2CH$), 2.21 (3H, s, C4–CH_3), 2.25 (6H, s, NMe_2), 2.48 (1H, dd, *J* 7.8, 16.2 Hz, Me_2N-CH_aH_b), 2.82 (1H, dd, *J* 3.6, 16.2 Hz, $Me_2NCH_aH_b$), 3.79 (1H, dd, *J* 7.8, 10.8 Hz, OCH_aH_b), 3.97 (2H, s, C6–H_2), 4.14 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.25–4.30 (1H, m, OCH_aH_b), 6.64 (1H, s, Ar–5-*H*), 6.68 (1H, d, *J* 8.4 Hz, Ar–*H*), 6.76 (1H, d, *J* 8.4 Hz, Ar–*H*). δ_C (150 MHz, $CDCl_3$) 14.4, 18.8, 29.8, 30.6, 40.3, 45.9, 59.4, 61.6, 69.2, 94.5, 117.2, 122.3, 122.8, 124.9, 138.8, 148.8, 149.2, 150.9, 166.3. LRMS (EI) *m*/*z* 372 (M^+). HRMS (EI): M^+, found 372.2148. $C_{20}H_{28}N_4O_3$ requires 372.2161.

*4.1.12.5. Ethyl 2-hexyl-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18e**).* Colorless crystals. 177–178 °C ($CHCl_3$). IR (KBr) 3234, 3155, 3084, 2956, 2929, 2873, 1706, 1608, 1247, 1105 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.2 Hz, $NHCH_2CH_2CH_2CH_2CH_3$), 1.26–1.30 (7H, m, OCH_2CH_3, $NHCH_2CH_2CH_2CH_2CH_2CH_3$), 1.39–1.43 (2H, m, $NHCH_2CH_2CH_2CH_2CH_2CH_3$), 1.65 (2H, tt, *J* 6.8, 6.8 Hz, $NHCH_2CH_2CH_2CH_2CH_2CH_3$), 2.37 (3H, s, C4–$CH_3$), 3.36 (2H, t, *J* 6.8 Hz, $NHCH_2CH_2CH_2CH_2CH_2CH_3$), 4.185 (2H, s, C6–$H_2$), 4.189 (2H, q, *J* 7.2 Hz, OCH_2CH_3). δ_C (100 MHz, $CDCl_3$) 14.0, 14.3, 17.8, 22.4, 26.3, 28.6, 31.3, 39.5, 42.3, 60.5, 98.6, 144.3, 151.3, 164.7. LRMS (EI) *m*/*z* 267 (M^+). HRMS (EI): M^+, found 267.1938. $C_{14}H_{25}N_3O_2$ requires 267.1947.

*4.1.12.6. Ethyl 2-benzyloxyamino-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18f**).* To a solution of **16f** (22.7 mg, 0.0584 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.5 mL, 6.7 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated, and added toluene and 4 M HCl in dioxane. This mixture was concentrated to give colorless powder, which was recrystallized from hexane/Et_2O to give corresponding HCl salt of **18f**: δ_H (400 MHz, CD_3OD) 1.27 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.26 (3H, s, C4–CH_3), 4.05 (2H, s, C6–H_2), 4.18 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.92 (2H, s, CH_2Ph), 7.39–7.42 (3H, m, Ar–*H*), 7.46–7.48 (2H, m, Ar–*H*). δ_C (100 MHz, CD_3OD) 14.5, 17.2, 40.3, 61.8, 80.3, 101.3, 129.7, 130.4, 131.0, 135.7, 145.1, 154.1, 165.9. This HCl salt was suspended in Et_2O, and 0.5 M NaOH was added. After separating the two layers, aqueous layer was extracted with Et_2O. Combined organic extracts was dried over Na_2SO_4, and concentrated to give compound **18f** (14.2 mg, 84%) as a colorless oil. IR (NaCl) 3332, 3219, 2981, 2933, 1671, 1496, 1246, 1097 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.30 (3H, s, C4–CH_3), 3.96 (2H, s, C6–H_2), 4.16 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.90 (2H, s, CH_2Ph), 5.52 (1H, br s, N*H*), 7.40 (5H, m, Ar–*H*), 9.52 (1H, br s, N*H*). ^{13}C NMR spectra could not be obtained due to the instability of the compound **18f**. LRMS (EI) *m*/*z* 289 (M^+). HRMS (EI): M^+, found 289.1407. $C_{15}H_{19}N_3O_3$ requires 289.1426.

*4.1.12.7. Ethyl 2-benzylamino-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18g**).* Colorless crystals. Mp 220–221 °C (MeOH). IR (KBr) 3068, 2879, 1704, 1670, 1542, 1279 cm^{-1}. δ_H (400 MHz, CD_3OD) 1.28 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.33 (3H, s, C4–CH_3), 4.12 (2H, s, C6–H_2), 4.20 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.48 (2H, s, CH_2Ph), 7.32–7.35 (3H, m, Ar–*H*), 7.40 (2H, s, Ar–*H*). δ_C (100 MHz, CD_3OD) 14.6, 17.7, 40.6, 46.2, 61.7, 100.9, 128.4, 129.3, 130.1, 136.8, 146.0, 152.7, 166.2. LRMS (FAB) *m*/*z* 274 (MH^+). HRMS (FAB): MH^+, found 274.1562. $C_{15}H_{20}N_3O_2$ requires 274.1556.

*4.1.12.8. Ethyl 2-pyrrolidyl-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**18h**).* Colorless prisms. Mp 119–121 °C (hexane/Et_2O). IR (KBr) 3504, 3357, 3261, 2977, 2877, 1654, 1590, 1471, 1214, 1078 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.92–1.96 (4H, m, $NCH_2CH_2CH_2CH_2$), 2.31 (3H, s, C4–CH_3), 3.42 (4H, br s, $NCH_2CH_2CH_2CH_2$), 4.14 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.47 (2H, br s, C6–H_2). δ_C (100 MHz, $CDCl_3$) 14.6, 23.8, 25.3, 41.1, 46.0, 59.0, 93.8, 153.6, 161.1, 167.2. LRMS (EI) *m*/*z* 237 (M^+). HRMS (EI): M^+, found 237.1493. $C_{12}H_{19}N_3O_2$ requires 237.1477.

4.2. Theoretical calculations

The initial geometry of 2-chloro-1,4-dihydropyrimidine-5-carboxylic acid **K** was derived from the crystal structure of **4** by replacing the methylsulfanyl and ethoxy carbonyl groups with chloro and carboxyl groups. Molecular modeling of 2-chloro-3,4-dihydropyrimidine-5-carboxylic acid **J**, 2-chloropyrimidine-5-carboxylic acid **L**, and aniline and theoretical conformational analysis of **J**, **L**, and aniline including **K** was carried out using AM1 semiempirical method incorporated into the Spartan program (Fig. S3).[17] Moreover, the gas phase geometry optimization of the molecules leading to energy minima was achieved using the B3LYP hybrid functional with the 6-311++G(d,p) basis set as implemented in the Gaussian 03 program package (Fig. S4).[18] For all optimized structures, vibrational normal mode analysis was carried out to ensure that the obtained structures were corresponding to minimum energy state. The frontier molecular orbitals of these compounds were then calculated of each minimum energy structure employing DFT calculations at the B3LYP/6-311++G(d,p) level of theory (Fig. S5). (1 Hartree=627.5095 kcal/mol).

Supplementary data

Characterization data (IR, ^{1}H NMR, ^{13}C NMR, LRMS, HRMS), X-ray crystallographic data of **4** and **17**, and copies of ^{1}H and ^{13}C NMR spectra of new compounds **1**, **2**, **4**, **7**, and **11**–**18** including HMBC of **4**, **13**, **15**, HSQC of **4**, NOE of **14** and **15**, the new synthetic procedure (six steps from *o*-fluorobenzyl bromide) of **11**. Theoretical calculations of 2-chloro-3,4(1,4)-dihydropyrimidine-5-carboxylic acid **J**, **K**, 2-chloropyrimidine-5-carboxylic acid **L**, and aniline. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.092.

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