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Synthesis of novel 2-phenyl-5-substituted dihydropyrimidines using 2-phenyl-1,3-diaza-1,3-butadienes and electron-deficient olefins

Yoshio Nishimura [a], Yoshizumi Yasui [b], Satoshi Kobayashi [c], Masahiko Yamaguchi [b,c], Hidetsura Cho [c,d,*]

[a] Faculty of Pharmacy, Yasuda Women's University, 6-13-1, Yasuhigashi, Asaminami-ku, Hiroshima 731-0153, Japan
[b] WPI Advanced Institute for Materials Research, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan
[c] Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan
[d] Graduate School of Science, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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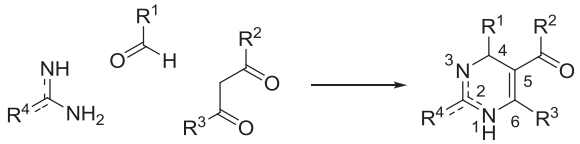
ABSTRACT

A novel synthetic method for 2,5-disubstituted dihydropyrimidines was developed. The cyclization of 1,3-diaza-4-dimethylamino-1,3-butadienes having a *N*-protecting group (*N*-Boc, *N*-Cbz, *N*-*n*-C_4H_9, *N*-Bn or *N*-Ph) with electron-deficient olefins, such as α,β-unsaturated carbonyl compounds, phenyl vinyl sulfone, and acrylonitrile was studied in detail. The cyclization smoothly proceeded to afford 4-dimethylamino-1,4,5,6-tetrahydropyrimidines or 1,6-dihydropyrimidines in good yields. The isolated 4-dimethylamino-1,4,5,6-tetrahydropyrimidines were converted to 2,5-disubstituted-1,6-dihydropyrimidines through the β-elimination of the dimethylamino group. 2,5-Disubstituted-1,4(6)-dihydropyrimidines were obtained after removal of the *N*-Boc or *N*-Cbz group. Independent tautomers of the resulting dihydropyrimidines were observed.

1. Introduction

Dihydropyrimidines have received continuous interest owing to their pharmaceutical activities, such as calcium antagonistic activity,[1] kinesin spindle protein (KSP) inhibitory activity,[2] and antimycobacterial activity.[3] Additionally, a new application has recently been reported in the field of materials sciences, that is, a corrosion inhibitor for austenitic stainless steel in acidic media.[4] Therefore, the development of useful synthetic methods for a variety of dihydropyrimidines may contribute to more pharmaceutical studies and lead to the discovery of attractive applications.

The construction of dihydropyrimidines has generally been performed by the condensation of amidine, guanidine or urea derivatives with aldehydes and 1,3-dicarbonyl compounds (Scheme 1).[5] To obtain a satisfactory yield by this method, it is preferred that the substituents R1, R2, and R3 be aromatic or alkyl groups.[6] Therefore, the obtained products are limited in terms of the substitution pattern. Much effort has been exerted to overcome this limitation so far.[7] We also reported the synthesis of 4-unsubstituted 2-aminodihydropyrimidines through nucleophilic substitution at position-2,[7c,d] and the derivatization of position-6 with Suzuki–Miyaura coupling.[8]



R^1, R^2, R^3 = alkyl, aryl
R^4 = O, S, OR', SR', NHR', H, CF_3, alkyl, aryl

Scheme 1. Typical construction of dihydropyrimidines by three-component condensation.

The nearly unsolved problem in this research area concerns the method of synthesizing less substituted dihydropyrimidines.[5a,b,d,9] It is hard to synthesize these compounds owing to polymerization of formaldehyde by the condensation method described above, and difficult to handle because of their instability toward oxidative atmosphere and acidic conditions.[10a–c] The alternative methods are the direct reduction of pyrimidine rings with complex metal hydrides[11a] and Et_3SiH/TFA,[11b] which however often give a mixture of dihydropyrimidines and tetrahydropyrimidines owing to over-reduction.

To develop a novel synthetic method for less substituted dihydropyrimidine rings, we designed the reactions of 1,3-diaza-1,3-butadienes with various olefinic compounds (Scheme 2).[12] The first step is the cyclization of 1,3-diaza-4-dimethylamino-1,3-butadiene **A** with electron-deficient olefin to give 1,4,5,6-tetrahydropyrimidine **B**. A protecting group (R) is attached at position-1 of 1,3-diaza-1,3-butadiene to stabilize itself as well as to control the reactivity

* Corresponding author. Tel.: +81 22 795 5501; fax: +81 22 795 5502; e-mail address: hcho@mail.pharm.tohoku.ac.jp (H. Cho).

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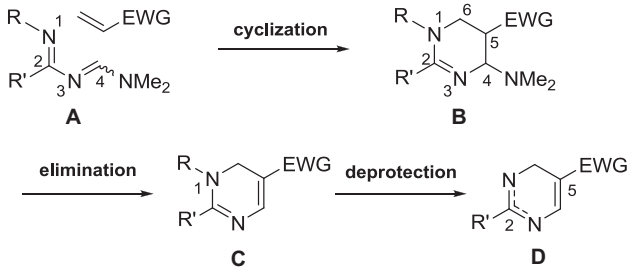
during cyclization. The resulting tetrahydropyrimidine **B** is converted to dihydropyrimidine **C** by the elimination of a dimethylamino group. Successive deprotection at position-1 of **C** affords the desired 2,5-disubstituted dihydropyrimidines **D**.



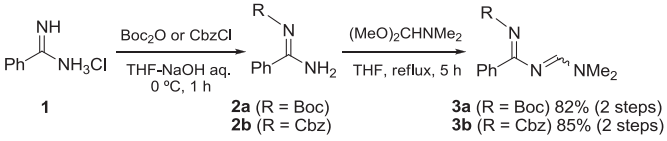
Scheme 2. Novel strategy for synthesis of 4,6-unsubstituted-2,5-disubstituted dihydropyrimidines **C** and **D**.

1,3-Diaza-4-dimethylamino-1,3-butadienes **A** are useful for the synthesis of pyrimidinone,[13] heterocyclic fused pyrimidinone,[14] or pyrimidine,[15] but have never been used for the synthesis of dihydropyrimidines.

Herein, we report the details of novel synthetic method of 2-phenyl-5-substituted dihydropyrimidines using 2-phenyl-1,3-diaza-1,3-butadienes and electron-deficient olefins.

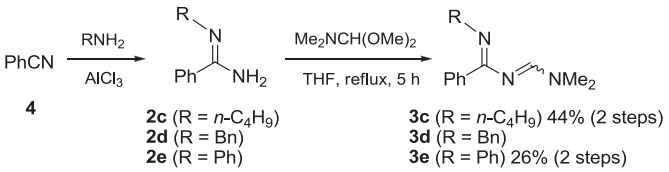
2. Result and discussion

We prepared five 1,3-diaza-4-dimethylamino-2-phenyl-1,3-butadienes having different substituents at position-N(1) to test their stability and reactivity. 1-*tert*-Butoxycarbonyl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadiene **3a** was prepared from phenylamidine hydrochloride **1** according to the reported procedure (Scheme 3).[15] The reaction of **1** and di-*tert*-butyl dicarbonate gave 1-*tert*-butoxycarbonyl phenylamidine **2a**, and the condensation of **2a** with dimethylformamide dimethyl acetal provided **3a**. The diazabutadiene **3a** was reported to be used for the following reaction without purification.[15] We also found out the purification of **3a** was troublesome; a mixture of decomposed material was obtained by distillation and conventional silica gel column chromatography. Finally, it was found out that the addition of a tertiary amine to the eluent of silica gel column chromatography prevents the decomposition and enables the purification of **3a** without any loss of the product. In a similar manner, novel 1-benzyloxycarbonyl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadiene **3b** was obtained as the sole product (Scheme 3).



Scheme 3. Preparation of 1-alkoxycarbonyl-1,3-diaza-1,3-butadienes **3a** and **3b**.

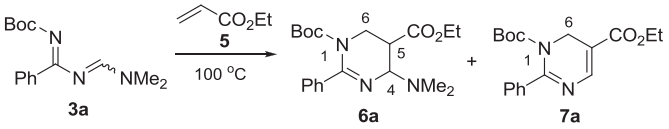
Novel 1-dimethylamino-3-phenyl-2,4-diaza-1,3-octadiene **3c** and 1-benzyl-1,3-diaza-4-dimethylamino-2-phenyl-1,3-butadienes **3d** as well as 1,3-diaza-4-dimethylamino-1,2-diphenyl-1,3-butadienes **3e** were prepared from *N*-substituted phenylamidines **2c**–**e**, which were synthesized from benzonitrile **4** in the presence of $AlCl_3$.[16] Condensation with dimethylformamide dimethyl acetal gave the desired 1,3-diaza-1,3-butadienes (Scheme 4). However, such electron-rich 1,3-diaza-1,3-butadienes were more unstable than **3a** and **3b**; **3c**–**e** could not be purified with silica gel even in the presence of tertiary amines. Therefore, **3c** and **3e** were purified through distillation and recrystallization, respectively. The 1-benzyl derivative **3d** was used in the following reaction without purification because of its instability.



Scheme 4. Preparation of 1-substituted 1,3-diaza-1,3-butadienes **3c**–**e**.

The cyclization was performed, in which **3a** (1.0 equiv) was treated with ethyl acrylate **5** (5.0 equiv) in DMA (*N*,*N*-dimethylacetamide) at 100 °C for 60 h. Although the reaction was very sluggish, 1-*tert*-butyl 5-ethyl 2-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate **7a** was produced in a low yield of 5% (Table 1, entry 1). The cyclization was performed in a variety of organic solvents to see what effect an organic solvent would have on the course of the reaction. When polar solvents, such as diglyme and DMI (1,3-dimethyl-2-imidazolidinone) were used, no cyclized products were detected (entries 2 and 3). TLC observation suggested a rapid decomposition of **3a** prior to the desired cyclization. In contrast, when less polar solvents, *o*-dichlorobenzene and toluene, were used, dihydropyrimidine **7a** was produced in 12% and 20% yields, respectively (entries 4 and 5). Moreover, when the reaction was run in mesitylene, the cyclization proceeded to give the desired 1-*tert*-butyl 5-ethyl 4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidine-1,5-dicarboxylate **6a** in 21% yield, accompanied by a small amount of **7a** in 3% yield and with the recovery (39%) of **3a** (entry 6). Again, it is worth noting that the addition of a tertiary amine is crucial for the good yield isolation of **6a** through silica gel column chromatography. When excess amounts of ethyl acrylate (10 and 30 equiv) were used, the yield of **6a** was increased to 41% and 78%, respectively (entries 7 and 8). Although tetrahydropyrimidine **6a** should be the intermediate of **7a**, prolonged reaction time did not affect the yield of **7a** (entry 9).

Table 1
Reaction conditions for cyclization reaction of **3a** and **5**

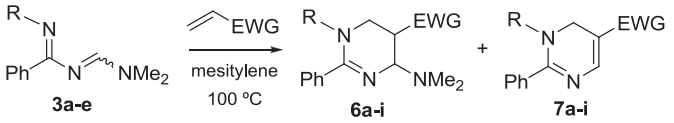


Entry	Solvent	Ethyl acrylate (equiv)	Time (h)	Yield (%)	
				6a	**7a**
1	DMA	3	60	—	5
2	Diglyme	3	60	—	—
3	DMI	3	60	—	—
4	*o*-$C_6H_4Cl_2$	3	60	—	12
5[a]	Toluene	5	12	—	20
6	Mesitylene	5	12	21	3
7	Mesitylene	10	13	41	2
8	Mesitylene	30	13	78	3
9	Mesitylene	30	24	74	4

[a] At reflux.

Under the optimized reaction conditions, a variety of substrates were subjected to cyclization (Table 2). The 1-benzyloxycarbonyl derivative **3b** was tolerated in the reaction without incident, and the corresponding tetrahydropyrimidine **6b** was obtained in 81% yield, accompanied by a small amount of **7b** (entry 2). Similarly, the 1-alkyl derivatives **3c** (R=*n*-C_4H_9) and **3d** (R=Bn) reacted smoothly with ethyl acrylate to afford the cyclized products **6c**/**7c** and **6d**/**7d** in high yields, respectively (entries 3 and 4). The yields of **6c**/**7c** and **6d**/**7d** were determined by ^{1}H NMR analysis because tetrahydropyrimidines **6c**/**6d** were partly converted to dihydropyrimidines **7c**/**7d** during silica gel chromatographic separation. In contrast, the

Table 2
Synthesis of tetrahydropyrimidine **6** and dihydropyrimidine **7**



Entry	Diene	R	EWG	Time (h)	Yield (%)	
					6	**7**
1	**3a**	Boc	CO_2Et	13	**6a**: 78	**7a**: 3
2	**3b**	Cbz	CO_2Et	24	**6b**: 81	**7b**: 3
3	**3c**	*n*-C_4H_9	CO_2Et	13	**6c**: 80[a]	**7c**: 8[a]
4[a]	**3d**	Bn	CO_2Et	13	**6d**: 60[b]	**7d**: 9[b]
5	**3e**	Ph	CO_2Et	24	—	—
6[c]	**3a**	Boc	CO_2Me	13	**6e**: 70	**7e**: 0
7[d]	**3a**	Boc	SO_2Ph	48	**6f**: 30	**7f**: 30
8[c]	**3a**	Boc	CN	13	**6g**: 29[a]	**7g**: 0
9[d]	**3a**	Boc	COC_6H_5	13	**6h**: 0	**7h**: 92
10[d]	**3a**	Boc	COC_6H_4Cl-*p*	13	**6i**: 0	**7i**: 91

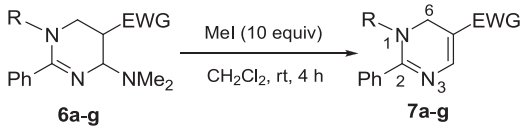
[a] Yields were determined by ^1H NMR analysis.
[b] Yields were determined by ^1H NMR analysis from benzonitrile **4** (three steps).
[c] Olefin (60.0 equiv) was used.
[d] Olefin (5.0 equiv) was used.

1-phenyl derivative **3e** gave no cyclized product (entry 5). In the case of phenyl vinyl sulfone and acrylonitrile, the products **6f**/**7f** and **6g** were obtained in modest yields (entries 7 and 8). The yield of **6g** was estimated by ^1H NMR analysis because of difficulty to separate **6g** from by-product. Remarkably, the reaction of **3a** with phenyl vinyl ketone[17] and *p*-chlorophenyl vinyl ketone[17] provided dihydropyrimidine **7h** and **7i** as the sole products without the formation of **6h** and **6i**, in 92% and 91% yield, respectively (entries 9 and 10). These results were supposed to be due to the effective β-elimination of the dimethylamino group from **6h** and **6i** supported by the high acidity of the α-hydrogen at C-5 enhanced by the carbonyl group. All the reactions in Table 2 gave only a single isomer of **6**/**7**, and the cyclization reaction proceeded regioselectively. The cyclization of **3a** with methyl vinyl ketone or diethyl vinylphosphonate did not work out, but gave a complex mixture or resulted in the recovery of **3a**, respectively.

Subsequently, the β-elimination of the NMe_2 group of the tetrahydropyrimidine derivative **6** was undertaken under various reaction conditions. The treatment of **6a** with acids, such as pyridinium *p*-toluenesulfonate, AcOH or TFA did not give any desired dihydropyrimidine **7a**, but resulted in a complex mixture. Next, Hoffmann elimination was performed.[18] When **6a** was reacted with MeI (15 equiv) and Et_3N (15 equiv) in CH_2Cl_2 for 24 h, dihydropyrimidine **7a** was obtained in 9% yield (Table 3, entry 1). It was found that the addition of Et_3N was not necessary, and that the β-elimination of the *N*,*N*-dimethylamino group of **6a** proceeded uneventfully to furnish dihydropyrimidine **7a** in 79% yield only with MeI (entry 2). Similarly, the reactions of **6b**, **6e**, **6f**, and **6g** with MeI afforded **7b**, **7e**, **7f**, and **7g** in good yields, respectively (entries 3, 6–8). However, this method was ineffective in the case of **6c** (R=*n*-C_4H_9): the linear amide **8c** was obtained in 34% yield with **7c** (20%) (entry 4 and footnote). Compound **8c** was possibly produced by the reaction of **7c** with excess MeI to give a quaternary ammonium salt at N-3 followed by the hydrolytic ring opening between positions C-2 and N-3. In the case of **7d** (R=Bn), a major product was also formed corresponding to the amide **8d** in 48% yield (entry 5). The electron-donating character at position-1 (alkyl groups) of **7c** and **7d** may cause the ring cleavage between positions 2 and 3, although an electron-withdrawing group (Boc group) causes the ring cleavage between positions 1 and 2 in another reaction, as described in our previous report.[7d]

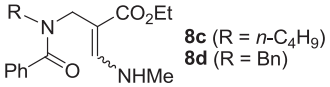
Subsequently, we investigated the reaction conditions for the effective β-elimination of the *N*,*N*-dimethylamino group of **6c**

Table 3
Elimination of NMe_2 group with MeI



Entry	Substrate	R	EWG	**7**: Yield (%)
1[a]	**6a**	Boc	CO_2Et	**7a**: 9
2	**6a**	Boc	CO_2Et	**7a**: 79
3	**6b**	Cbz	CO_2Et	**7b**: 84
4[b]	**6c**	*n*-C_4H_9	CO_2Et	**7c**: 20
5[c]	**6d**	Bn	CO_2Et	**7d**: 32
6	**6e**	Boc	CO_2Me	**7e**: 88
7[d]	**6f**	Boc	SO_2Ph	**7f**: 81
8	**6g**	Boc	CN	**7g**: 21[e]

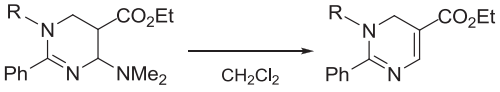
[a] Triethylamine (15 equiv) and MeI (15 equiv) were used for 24 h.
[b] A mixture of **6c** and **7c** (11.9:1 by ^1H NMR analysis) was reacted. Compound **8c** was obtained in 34% yield.
[c] A mixture of **6d** and **7d** (8.6:1 by ^1H NMR analysis) was reacted. Compound **8d** was obtained in 48% yield.



[d] MeI (40 equiv) was used for 15 h.
[e] Yield from **3a**.

(Table 4). Decreasing the amount of MeI (1.3 equiv) resulted in a low yield of **7c** (entry 1). The use of aluminum oxide (1000 wt %) also resulted in a low yield of **7c** (entry 2). However, when **6c** was treated with silica gel (1000 wt %) in CH_2Cl_2 for 7.5 h, **7c** was obtained in a modest yield (54%) accompanied by an unidentified by-product (entry 3). The by-product might have been derived from the hydrolysis of the product. Therefore, the addition of molecular sieves to the reaction was tested. Finally, when **6c** was treated with silica gel (1000 wt %) in the presence of MS 3 Å (50 wt %), **7c** was obtained in 84% yield (entry 4). The other dihydropyrimidine **7d** was obtained in 71% yield under the same conditions (entry 5).

Table 4
Elimination of NMe_2 group from tetrahydropyrimidine **6c** and **6d**[a]

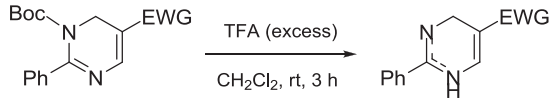


Entry	Substrate	Conditions	**7**: Yield (%)
1[b]	**6c**	Iodomethane (1.3 equiv), rt, 4 h	**7c**: 20
2	**6c**	Aluminum oxide (1000 wt %), rt, 12 h then reflux, 4 h	**7c**: 21
3	**6c**	Silica gel (1000 wt %), rt, 7.5 h	**7c**: 54
4	**6c**	Silica gel (1000 wt %), MS 3 Å (50 wt %), rt, 21 h	**7c**: 84
5	**6d**	Silica gel (1000 wt %), MS 3 Å (50 wt %), rt, 16 h	**7d**: 71

[a] A mixture of **6c**/**7c** (11.9:1 by ^1H NMR analysis) or **6d**/**7d** (8.6:1 by ^1H NMR analysis) was reacted.
[b] Compound **8c** was formed in 38% yield.

Finally, 2,5-disubstituted dihydropyrimidines were obtained by removing the protecting groups. 1-Boc groups were cleaved smoothly under acidic conditions (Table 5). Compound **7a** was treated with excess TFA in CH_2Cl_2 at room temperature for 3 h to afford ethyl 2-phenyl-4,6-unsubstituted dihydropyrimidine-5-carboxylate **9a** in 97% yield (entry 1). The deprotection reactions

Table 5
Cleavage of 1-Boc group from dihydropyrimidines **7a**, **e**–**f**, **i**

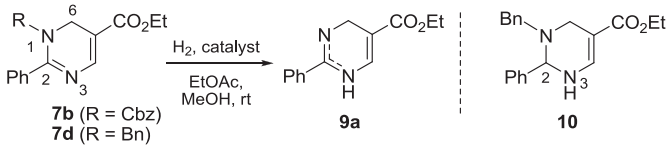


Entry	Substrate	EWG	**9**: Yield (%)
1	**7a**	CO_2Et	**9a**: 97
2	**7e**	CO_2Me	**9e**: 99
3	**7f**	SO_2Ph	**9f**: 98
4	**7i**	COC_6H_4Cl-*p*	**9i**: 100

of **7e**–**f**, **i** with TFA uneventfully proceeded to afford the desired dihydropyrimidines **9e**–**f**, **i** (entries 2–4).

Subsequently, the deprotection of other 1-substituents was carried out (Table 6). The 1-benzyloxy derivative **7b** was treated with 10% Pd/C (20 wt %) under a hydrogen atmosphere (1 atm) in EtOAc/MeOH at room temperature for 18 h to give **9a** in 89% yield (entry 1). On the other hand, the cleavage of 1-Bn group to give dihydropyrimidines was not feasible: hydrogenolysis did not proceed with 10% Pd/C (entry 2). In the case of using 20% $Pd(OH)_2/C$, tetrahydropyrimidine **10** was isolated as a result of an undesired reduction of the 2,3-double bond (entry 3).

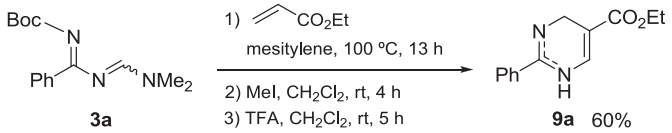
Table 6
Reductive removal of protecting groups from dihydropyrimidines **7b** and **7d**



Entry	Substrate	R	Catalyst	**9**:Yield (%)
1	**7b**	Cbz	10% Pd/C (20 wt %)	89
2	**7d**	Bn	10% Pd/C (20 wt %)	—[a]
3	**7d**	Bn	20% $Pd(OH)_2/C$ (40 wt %)	—[b]

[a] The starting material was recovered intact.
[b] Tetrahydropyrimidine **10** was isolated in 33% yield.

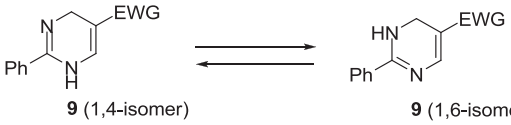
A more effective procedure for synthesizing dihydropyrimidine **9a** from **3a** was examined without isolating **6a** and **7a** after cyclization, followed by the treatment of MeI and TFA. Consequently, a three-step successive reaction was conveniently realized to afford **9a** in 60% overall yield, as shown in Scheme 5.



Scheme 5. Three-step synthesis of **9a** without isolating **6a** and **7a**.

The synthesized dihydropyrimidines **9** showed an interesting behavior in their ^1H NMR spectra (600 MHz).[5c,e,7c,10d,12] For instance, **9a** was observed as a single isomer in $CDCl_3$ and CD_3OD, and two independent isomers existed at a ratio of 2.3:1.0 in DMSO-d_6 (Fig. 1, Table 7, entry 1). The observed signals of NH protons [δ 9.48 (major), 8.43 (minor)] and methylene protons [δ 4.32 (major), 4.21 (minor)] in DMSO-d_6 indicated that the two isomers were 1,4- and 1,6-tautomers. The major isomer was assigned to the 1,4-isomer because the vinyl proton (δ 7.18) was observed as a doublet peak (J 5.4 Hz) by coupling with an NH proton. The reason for the spectral difference depending on the solvent was probably the rapid isomerization between the two tautomers of **9a** that occurred in $CDCl_3$ or CD_3OD compared with that in DMSO-d_6 (Fig. 1). To determine the effect of a solvent on the existence of dihydropyrimidines, we measured the ^1H NMR spectra of **9f** and **9i** in CD_3OD, $CDCl_3$, and DMSO-d_6 (0.01 M, 25 °C). Although both **9f** and **9i** were observed as a single isomer in CD_3OD, independent tautomers of **9f** (2.9:1.0 in $CDCl_3$; 3.5:1.0 in DMSO-d_6) and **9i** (1.9:1.0 in $CDCl_3$; 1.5:1.0 in DMSO-d_6) were observed in $CDCl_3$ and DMSO-d_6, respectively (Table 7, entries 2 and 3). Thus, it was found that all dihydropyrimidines **9** existed as independent tautomers in DMSO-d_6 at a ratio of 1.5–3.5:1.0.

Table 7
Ratios of tautomers **9** in ^1H NMR spectra (0.01 M, 25 °C)



Entry	Substrate	EWG	Solvent		
			CD_3OD	$CDCl_3$	DMSO-d_6
1	**9a**	CO_2Et	Single	Single	2.3:1.0
2	**9f**	SO_2Ph	Single	2.9:1.0	3.5:1.0
3	**9i**	COC_6H_4Cl-*p*	Single	1.9:1.0	1.5:1.0

3. Conclusion

A stepwise approach to synthesizing 2,5-disubstituted dihydropyrimidines has been developed. A variety of 1,3-diaza-1,3-butadienes having different substituents at position-1 were synthesized and subjected to cyclization with electron-deficient olefins. The cyclization proceeded smoothly to give 4-dimethylamino-1,4,5,6-tetrahydropyrimidines and/or 1-protecting-2,5-disubstituted-1,6-dihydropyrimidines. The ratio of both compounds was found to depend on the type of electron-deficient olefin. The reactions of 1,3-diaza-1,3-butadienes with acrylates mainly afforded tetrahydropyrimidines and the reaction with vinyl sulfone yielded a 1:1 ratio of both compounds. Remarkably, the reaction with aryl vinyl ketones provided dihydropyrimidines as the sole products without giving tetrahydropyrimidines. The isolated 4-dimethylamino–1,4,5,6-tetrahydro pyrimidines were converted to 1,6-dihydropyrimidines through the β-elimination of the dimethylamino group under MeI or silica gel treatment. The cleavage of the 1-Boc and 1-Cbz group afforded 2,5-disubstituted-4(6)-dihydropyrimidines. In addition, a three-step successive reaction from 1,3-diaza-1,3-butadiene without purification of the intermediate was conveniently realized to afford 1,4(6)-dihydropyrimidine in high overall yield.

Through this study, 2,5-disubstituted-1,6-dihydropyrimidines have been made accessible in an efficient manner. This achievement may lead to further application of dihydropyrimidines in many fields including heterocyclic chemistry and pharmaceutical sciences.

4. Experimental section

4.1. General

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 (300, 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,

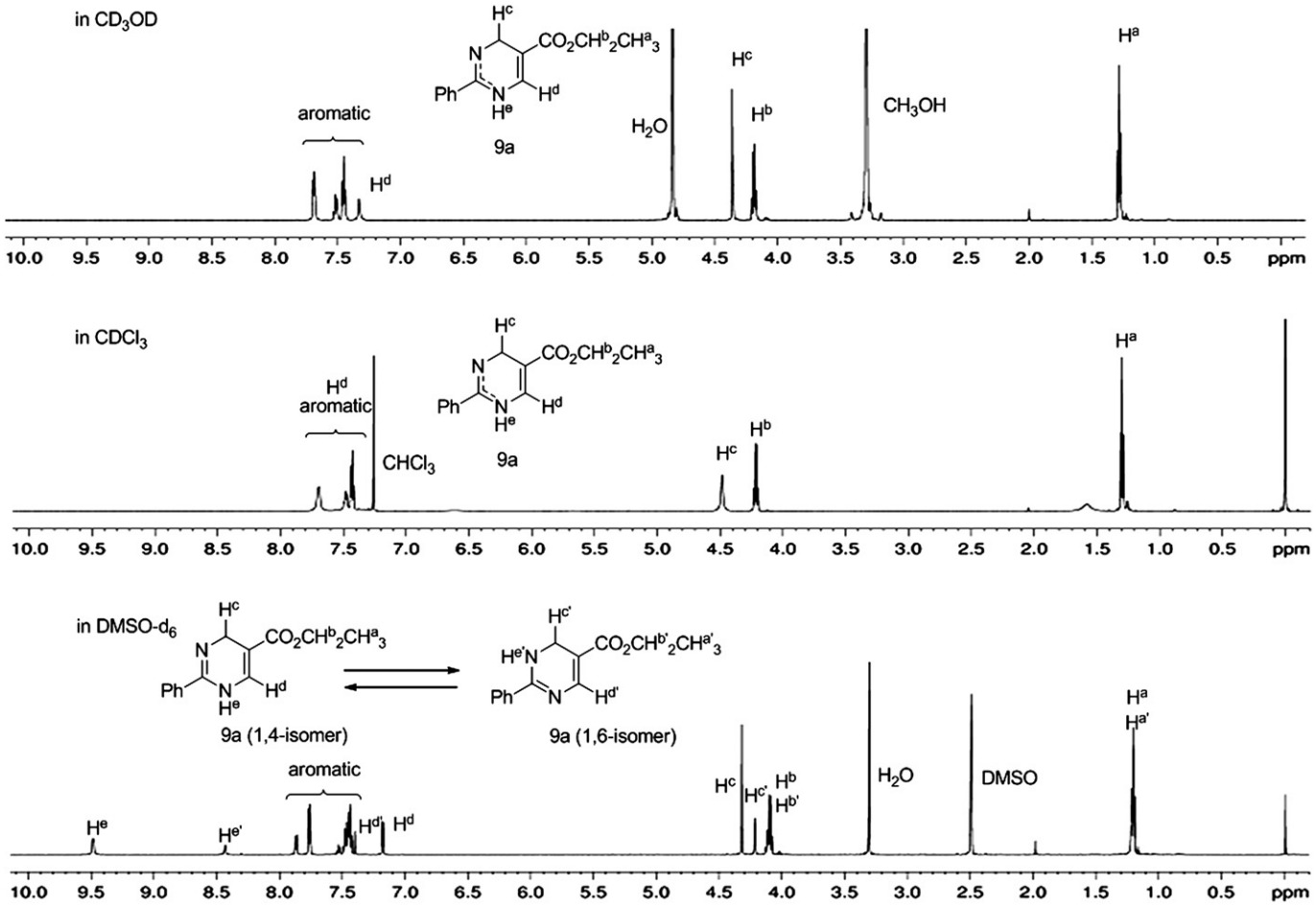


Fig. 1. ^{1}H NMR spectra of **9a** in CD_3OD, $CDCl_3$, and DMSO-d_6 (600 MHz, 0.01 M, 25 °C).

quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a Varian Mercury (75, 100 MHz) or a Bruker AVANCE III 600 (150 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. 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).

4.2. Preparation of 1,3-diaza-1,3-butadiene 3

*4.2.1. 1-tert-Butoxycarbonyl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadiene (**3a**).* To a suspension of phenylamidine hydrochloride **1** (3.12 g, 19.9 mmol) in THF (40 mL) was dropwise added a solution of NaOH (2.00 g, 50.0 mmol) in H_2O (40 mL) at 0 °C. Di-*tert*-butyl dicarbonate (4.40 g, 20.2 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h, and EtOAc (150 mL) was added. The organic layer was separated, and washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give *N*-*tert*-butoxycarbonyl phenylamidine **2a** (3.81 g). To a solution of crude **2a** (3.81 g) in anhyd THF (35 mL) was added dimethylformamide dimethyl acetal (3.00 mL, 22.6 mmol) under an argon atmosphere. The reaction mixture was stirred at reflux for 5 h, and EtOAc (100 mL) was added. The organic layer was washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (toluene/EtOAc/Et_3N=85:10:5) to afford **3a** (4.51 g, 16.4 mmol, 82% for two steps) as a colorless oil; IR (neat) cm^{-1}: 2977, 1703, 1633, 1591, 1570, 1242, 1160; δ_H (600 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 3.06 (3H, s, N*Me*), 3.09 (3H, s, N*Me*), 7.36 (2H, t, *J* 7.2 Hz, Ar–*m*-*H*), 7.41 (1H, tt, *J* 1.2, 7.2 Hz, Ar–*p*-*H*), 7.41 (2H, dd, *J* 1.2, 7.2 Hz, Ar–*o*-*H*), 7.98 (1H, s, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 27.9, 34.6, 40.6, 80.2, 127.9, 128.6, 130.5, 136.5, 155.6, 162.1, 165.7; *m*/*z* (EI) 275 (M^+); HRMS (EI): M^+, found 275.1621. $C_{15}H_{21}N_3O_2$ requires 275.1633.

*4.2.2. 1-Benzyloxycarbonyl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadiene (**3b**).* Compound **3b** was prepared in a similar manner to **3a** as described above. Pale yellow oil; IR (neat) cm^{-1}: 2929, 1703, 1633, 1588, 1569, 1219, 1091; δ_H (600 MHz, $CDCl_3$) 2.93 (3H, s, N*Me*), 3.01 (3H, s, N*Me*), 5.18 (2H, s, CH_2Ph), 7.27–7.38 (7H, m, Ar–*H*), 7.41 (1H, t, *J* 7.8 Hz, Ar–*p*-*H*), 7.81 (2H, d, *J* 7.8 Hz, Ar–*o*-*H*), 7.88 (1H, s, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 34.6, 40.6, 67.3, 127.8, 128.0, 128.2, 128.4, 128.6, 130.8, 136.3, 136.4, 155.9, 162.8, 166.8; *m*/*z* (EI) 309 (M^+); HRMS (EI): M^+, found 309.1481. $C_{18}H_{19}N_3O_2$ requires 309.1477.

*4.2.3. 1-Dimethylamino-3-phenyl-2,4-diaza-1,3-octadiene (**3c**).* To anhyd aluminum chloride (3.00 g, 22.5 mmol) was added benzonitrile **4** (2.10 mL, 20.5 mmol) dropwise at room temperature under an argon atmosphere. After cooled to room temperature, *n*-butylamine (2.50 mL, 25.1 mmol) was added, and the reaction mixture was heated at 100 °C for 12 h. The mixture was poured slowly into a stirred mixture of concentrated hydrochloric acid (0.6 mL) and water (30 mL), and the suspension was stirred for 20 min and filtered through a Celite. The filtrate was basified with 2 M NaOH aqueous solution, and the aqueous layer was extracted with chloroform three times. The combined organic layer was washed with

brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give *N*-*n*-butyl phenylamidine **2c** (3.15 g). To a solution of crude **2c** (1.32 g) in anhyd THF (15 mL) was added dimethylformamide dimethyl acetal (1.50 mL, 11.3 mmol) under an argon atmosphere. The reaction mixture was stirred at reflux for 12 h. After concentrated under reduced pressure, the residue was distilled in vacuo to give **3c** (881 mg, 3.81 mmol, 44% for two steps) as a yellow oil; IR (neat) cm^{-1}: 2926, 1643, 1596, 1574, 1371, 1087, 705; δ_H (600 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.42 (2H, tq, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.65 (2H, tt, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 2.95 (3H, s, N*Me*), 3.05 (3H, s, N*Me*), 3.50 (2H, t, *J* 7.2 Hz, $CH_2CH_2CH_2CH_3$), 7.31 (1H, s, 4-C*H*), 7.32–7.35 (3H, m, Ar–*H*), 7.62–7.67 (2H, m, Ar–*H*); δ_C (150 MHz, $CDCl_3$) 14.1, 20.9, 33.5, 34.0, 40.0, 49.0, 128.0, 128.2, 128.8, 139.3, 154.0, 163.0; *m*/*z* (EI) 231 (M^+); HRMS (EI): M^+, found 231.1728. $C_{14}H_{21}N_3$ requires 231.1735.

*4.2.4. N-Benzyl phenylamidine (**2d**).* Compound **2d** was prepared in a similar manner to **2c** as described above. Pale yellow crystals; mp 54–56 °C (*n*-hexane/chloroform); IR (neat) cm^{-1}: 3303, 1604, 1568, 1552, 696; δ_H (600 MHz, DMSO-d_6) 4.33 (2H, s, CH_2Ph), 6.20–6.60 (2H, br s, NH_2), 7.19 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.31 (2H, t, *J* 7.2 Hz, Ar–*m*-*H*), 7.35–7.50 (5H, m, Ar–*H*), 7.70–7.95 (2H, br s, Ar–*H*); δ_C (150 MHz, DMSO-d_6) 49.5 (br), 126.2, 126.7, 127.6, 128.1, 128.2, 129.5, 137.4, 142.1, 156.8 (br); *m*/*z* (EI) 210 (M^+); HRMS (EI): M^+, found 210.1137. $C_{14}H_{14}N_2$ requires 210.1157.

*4.2.5. 4-Dimethylamino-1,2-diphenyl-1,3-diaza-1,3-butadiene (**3e**).* Compound **3e** was prepared in a similar manner to **3c** as described above, and purified by recrystallization from *n*-hexane/EtOAc as a mixture of isomers (2.3:1.0). Pale yellow crystals; mp 101 °C (*n*-hexane/EtOAc); IR (neat) cm^{-1}: 1638, 1602, 1588, 1572, 1373, 1051, 706; δ_H (600 MHz, $CDCl_3$) 2.80 (3H, s, N*Me*), 2.91 (3H, s, N*Me*), 3.11* (s, N*Me*), 3.12* (s, N*Me*), 6.71* (d, *J* 7.2 Hz, Ar–*o*-*H*), 6.88* (t, *J* 7.2 Hz, Ar–*p*-*H*), 6.96 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.02 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*), 7.11* (t, *J* 7.2 Hz, Ar–*p*-*H*), 7.15–7.29* (2H, m, Ar–*H*), 7.30* (d, *J* 6.6 Hz, Ar–*o*-*H*), 7.34 (1H, s, 4-C*H*), 7.37–7.50 (3H, m, Ar–*H*), 7.93 (2H, d, *J* 6.6 Hz, Ar–*o*-*H*), 8.29* (s, 4-C*H*) (*Peaks of minor isomer); δ_C (150 MHz, $CDCl_3$) 34.0, 34.9, 39.9, 40.8, 121.8, 122.0, 122.6, 127.6, 128.0, 128.2, 128.4, 128.50, 128.54, 129.5, 129.8, 136.2, 138.4, 150.6, 151.1, 155.0, 156.0, 162.3, 164.8; *m*/*z* (EI) 251 (M^+); HRMS (EI): M^+, found 251.1415. $C_{16}H_{17}N_3$ requires 251.1423.

4.3. General procedure for cyclization reaction of 1,3-diaza-1,3-butadiene 3 with olefins for synthesis of 6a–f

*4.3.1. 1-tert-Butyl 5-ethyl 4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidine-1,5-dicarboxylate (**6a**).* A solution of **3a** (208 mg, 0.757 mmol) and ethyl acrylate **5** (2.50 mL, 23.0 mmol) in mesitylene (6 mL) was heated at 100 °C for 13 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=30:5:1 to 30:30:1) to afford **6a** (222 mg, 0.591 mmol, 78%) and **7a** (7.4 mg, 0.022 mmol, 3%). *Compound* **6a**: Colorless crystals; mp 103 °C (*n*-hexane/Et_2O); IR (KBr) cm^{-1}: 2984, 1735, 1712, 1614, 1348; δ_H (600 MHz, $CDCl_3$) 1.12 (9H, s, CMe_3), 1.29 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.42 (6H, s, NMe_2), 2.84 (1H, ddd, *J* 6.6, 9.6, 10.8 Hz, 5-C*H*), 3.78 (1H, dd, *J* 10.8, 12.0 Hz, 6-C*H*), 3.97 (1H, dd, *J* 6.6, 12.0 Hz, 6-C*H*), 4.18–4.27 (2H, m, OCH_2CH_3), 4.35 (1H, d, *J* 9.6 Hz, 4-C*H*), 7.32–7.40 (3H, m, Ar–*H*), 7.51 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*); δ_C (150 MHz, $CDCl_3$) 14.1, 27.5, 40.2, 44.6, 45.1, 61.0, 77.6, 82.2, 127.0, 127.9, 129.4, 138.3, 152.7, 154.3, 171.5; *m*/*z* (EI) 375 (M^+); HRMS (EI): M^+, found 375.2163. $C_{20}H_{29}N_3O_4$ requires 375.2158.

*4.3.2. 1-Benzyl 5-ethyl 4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidine-1,5-dicarboxylate (**6b**).* Colorless crystals; mp 73–74 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 2866, 1736, 1620, 1276, 1195; δ_H (600 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.40 (6H, s, NMe_2), 2.86 (1H, ddd, *J* 6.6, 9.6, 10.8 Hz, 5-C*H*), 3.91 (1H, dd, *J* 10.8, 12.0 Hz, 6-C*H*), 3.93 (1H, dd, *J* 6.6, 12.0 Hz, 6-C*H*), 4.17–4.28 (2H, m, OCH_2CH_3), 4.33 (1H, d, *J* 9.6 Hz, 4-C*H*), 4.97 (2H, s, CH_2Ph), 6.87 (2H, d, *J* 7.8 Hz, Ar–*o*-*H*), 7.21 (2H, t, *J* 7.8 Hz, Ar–*m*-*H*), 7.23–7.28 (1H, m, Ar–*p*-*H*), 7.32 (2H, t, *J* 7.8 Hz, Ar–*m*-*H*), 7.38 (1H, t, *J* 7.8 Hz, Ar–*p*-*H*), 7.52 (2H, d, *J* 7.8 Hz, Ar–*o*-*H*); δ_C (150 MHz, $CDCl_3$) 14.1, 40.2, 44.7, 45.5, 61.1, 68.3, 77.7, 127.0, 128.0, 128.10, 128.14, 128.3, 129.7, 134.8, 137.2, 153.7, 153.9, 171.3; *m*/*z* (EI) 409 (M^+); HRMS (EI): M^+, found 409.2002. $C_{23}H_{27}N_3O_4$ requires 409.2001.

*4.3.3. Ethyl 1-butyl-4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidine-5-carboxylate (**6c**).* Pale yellow oil containing small amounts of **7c** (**6c**/**7c**=11.9:1); IR (neat) cm^{-1}: 2960, 1731, 1608, 1599, 1577, 1375, 1178; δ_H (600 MHz, $CDCl_3$) 0.78 (3H, t, *J* 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.12 (2H, tq, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.29 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.45 (2H, tt, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 2.38 (6H, s, NMe_2), 2.77 (1H, ddd, *J* 4.2, 9.6, 10.8 Hz, 5-C*H*), 2.95 (1H, dt, *J* 7.2, 14.4 Hz, C*H*$CH_2CH_2CH_3$), 3.04 (1H, dt, *J* 7.2, 14.4 Hz, C*H*$CH_2CH_2CH_3$), 3.29 (1H, dd, *J* 4.2, 12.0 Hz, 6-C*H*), 3.57 (1H, dd, *J* 10.8, 12.0 Hz, 6-C*H*), 4.17–4.27 (2H, m, OCH_2CH_3), 4.35 (1H, d, *J* 9.6 Hz, 4-C*H*), 7.32–7.43 (5H, m, Ar–*H*); δ_C (150 MHz, DMSO-d_6) 13.6, 14.2, 19.2, 29.8, 39.7, 41.1, 47.2, 51.0, 60.2, 76.6, 128.0, 128.1, 128.7, 137.7, 157.6, 172.4; *m*/*z* (EI) 331 (M^+); HRMS (EI): M^+, found 331.2249. $C_{19}H_{29}N_3O_2$ requires 331.2260.

*4.3.4. Ethyl 1-benzyl-4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidine-5-carboxylate (**6d**).* Yellow oil containing small amounts of **7d** (**6d**/**7d**=8.6:1); IR (neat) cm^{-1}: 2977, 1729, 1609, 1599, 1265, 1184, 701; δ_H (600 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.39 (6H, s, NMe_2), 2.72 (1H, ddd, *J* 4.2, 9.6, 10.8 Hz, 5-C*H*), 3.22 (1H, dd, *J* 4.2, 12.0 Hz, 6-C*H*), 3.50 (1H, dd, *J* 10.8, 12.0 Hz, 6-C*H*), 4.10–4.20 (2H, m, OCH_2CH_3), 4.22 (1H, d, *J* 15.6 Hz, PhC*H*), 4.32 (1H, d, *J* 15.6 Hz, PhC*H*), 4.40 (1H, d, *J* 9.6 Hz, 4-C*H*), 7.19 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*), 7.25–7.55 (8H, m, Ar–*H*); δ_C (150 MHz, $CDCl_3$) 14.0, 39.8, 40.9, 47.4, 55.6, 60.6, 76.6, 127.0, 127.4, 128.1, 128.3, 128.7, 129.1, 137.0, 137.2, 158.5, 172.6; *m*/*z* (EI) 365 (M^+); HRMS (EI): M^+, found 365.2088. $C_{22}H_{27}N_3O_2$ requires 365.2103.

*4.3.5. 1-tert-Butyl 5-methyl 4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidine-1,5-dicarboxylate (**6e**).* Colorless crystals; mp 119 °C (*n*-hexane/Et_2O); IR (KBr) cm^{-1}: 2976, 2875, 1739, 1624, 1350; δ_H (400 MHz, $CDCl_3$) 1.12 (9H, s, CMe_3), 2.42 (6H, s, NMe_2), 2.87 (1H, ddd, *J* 6.0, 9.6, 10.8 Hz, 5-C*H*), 3.77 (3H, s, OCH_3), 3.78 (1H, dd, *J* 10.8, 12.0 Hz, 6-C*H*), 3.97 (1H, dd, *J* 6.0, 12.0 Hz, 6-C*H*), 4.37 (1H, d, *J* 9.6 Hz, 4-C*H*), 7.32–7.41 (3H, m, Ar–*H*), 7.52 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*); δ_C (100 MHz, $CDCl_3$) 27.5, 40.2, 44.5, 45.0, 52.3, 77.6, 82.3, 127.0, 127.9, 129.5, 138.2, 152.7, 154.4, 172.0; *m*/*z* (EI) 361 (M^+); HRMS (EI): M^+, found 361.2009. $C_{19}H_{27}N_3O_4$ requires 361.2002.

*4.3.6. tert-Butyl 4-dimethylamino-2-phenyl-5-phenylsulfonyl-1,4,5,6-tetrahydropyrimidine-1-carboxylate (**6f**).* Yellow amorphous; IR (KBr) cm^{-1}: 2977, 1719, 1628, 1146; δ_H (600 MHz, $CDCl_3$) 1.14 (9H, s, CMe_3), 2.23 (6H, s, NMe_2), 3.54 (1H, ddd, *J* 6.0, 7.2, 7.8 Hz, 5-C*H*), 3.83 (1H, dd, *J* 6.0, 13.8 Hz, 6-C*H*), 4.15 (1H, dd, *J* 7.8, 13.8 Hz, 6-C*H*), 4.67 (1H, d, *J* 7.2 Hz, 4-C*H*), 7.35 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*), 7.40 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.53 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*), 7.58 (2H, d, *J* 7.8 Hz, Ar–*o*-*H*), 7.67 (1H, t, *J* 7.8 Hz, Ar–*p*-*H*), 8.01 (2H, d, *J* 7.8 Hz, Ar–*o*-*H*); δ_C (150 MHz, $CDCl_3$) 27.4, 39.6, 40.8, 62.2, 73.6, 82.6, 127.2, 127.9, 128.9, 129.2, 129.9, 133.8, 137.4, 138.2, 152.3, 155.1; *m*/*z* (EI) 443 (M^+); HRMS (EI): M^+, found 443.1883. $C_{23}H_{29}N_3O_4S$ requires 443.1879.

4.4. General procedure for elimination of NMe_2 group of 6a–g using MeI for synthesis of 7a–g

*4.4.1. 1-tert-Butyl 5-ethyl 2-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (**7a**).* To a solution of **6a** (75.0 mg, 0.200 mmol) in

CH_2Cl_2 (2 mL) was added MeI (0.130 mL, 2.09 mmol) dropwise at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 4 h, and triethylamine (0.5 mL), EtOAc (20 mL), water (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL×2). The combined organic layer was washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=100:10:1) to afford **7a** (52.2 mg, 0.158 mmol, 79%) as yellow crystals; mp 107 °C (*n*-hexane); IR (KBr) cm^{-1}: 2986, 1721, 1699, 1529, 1284, 1153; δ_H (600 MHz, $CDCl_3$) 1.12 (9H, s, C*Me*$_3$), 1.34 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 4.28 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.52 (2H, d, *J* 1.2 Hz, 6-C*H*$_2$), 7.41 (2H, t, *J* 7.2 Hz, Ar—*m*-*H*), 7.48 (1H, t, *J* 7.2 Hz, Ar—*p*-*H*), 7.65 (2H, d, *J* 7.2 Hz, Ar—*o*-*H*), 7.70 (1H, d, *J* 1.2 Hz, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 14.3, 27.4, 40.2, 60.8, 83.1, 115.6, 128.2, 128.5, 131.0, 136.8, 143.1, 152.0, 158.2, 164.8; *m*/*z* (EI) 330 (M^+); HRMS (EI): M^+, found 330.1570. $C_{18}H_{22}N_2O_4$ requires 330.1580.

*4.4.2. 1-Benzyl 5-ethyl 2-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (**7b**).* Yellow oil; IR (neat) cm^{-1}: 2982, 1725, 1537, 1281, 1230, 1184; δ_H (600 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 4.28 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.59 (2H, d, *J* 1.2 Hz, 6-C*H*$_2$), 4.99 (2H, s, C*H*$_2$Ph), 6.83 (2H, d, *J* 7.2 Hz, Ar—*o*-*H*), 7.19 (2H, t, *J* 7.2 Hz, Ar—*m*-*H*), 7.24 (1H, t, *J* 7.8 Hz, Ar—*p*-*H*), 7.37 (2H, t, *J* 7.8 Hz, Ar—*m*-*H*), 7.46 (1H, t, *J* 7.2 Hz, Ar—*p*-*H*), 7.65 (2H, d, *J* 7.8 Hz, Ar—*o*-*H*), 7.70 (1H, d, *J* 1.2 Hz, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 14.2, 40.7, 60.8, 68.7, 115.9, 127.9, 128.2, 128.3, 128.4, 128.5, 131.3, 134.4, 135.7, 143.0, 153.4, 157.2, 164.6; *m*/*z* (EI) 364 (M^+); HRMS (EI): M^+, found 364.1433. $C_{21}H_{20}N_2O_4$ requires 364.1423.

*4.4.3. Ethyl 1-butyl-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (**7c**).* Compound **7c** was obtained in 20% yield, accompanied by amide **8c** (34%) (Table 3, entry 4). *Compound* **7c**: Yellow oil; IR (neat) cm^{-1}: 2960, 2933, 1693, 1622, 1514, 1444, 1262, 1101; δ_H (600 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.18 (2H, tq, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.31 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 1.57 (2H, tt, *J* 7.2, 7.8 Hz, $CH_2CH_2CH_2CH_3$), 3.16 (2H, t, *J* 7.8 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$), 4.23 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.33 (2H, s, 6-C*H*$_2$), 7.38—7.45 (5H, m, Ar—*H*), 7.50 (1H, s, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 13.5, 14.4, 19.6, 29.0, 45.6, 52.4, 60.0, 104.2, 127.8, 128.5, 129.9, 135.4, 146.2, 163.5, 166.3; *m*/*z* (EI) 286 (M^+); HRMS (EI): M^+, found 286.1686. $C_{17}H_{22}N_2O_2$ requires 286.1681.

*4.4.4. N-Butyl-N-[(2-ethoxycarbonyl-3-methylamino)-prop-2-en-1-yl]benzamide (**8c**).* Colorless crystals; mp 63—63 °C (*n*-hexane); IR (neat) cm^{-1}: 2953, 1687, 1629, 1434, 1266, 1134, 1098; δ_H (600 MHz, $CDCl_3$) 0.77 (3H, t, *J* 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.12 (2H, tq, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.28 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 1.60 (2H, tt, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2CH_3$), 3.00 (3H, d, *J* 4.8 Hz, NHC*H*$_3$), 3.19 (2H, t, *J* 7.2 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$), 4.16 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.43 (2H, s, NC*H*$_2$), 7.28—7.43 (6H, m, Ar—*H*, N*H*), 7.56 (1H, d, *J* 13.8 Hz, CH$_3$NHC*H*); δ_C (150 MHz, $CDCl_3$) 13.5, 14.6, 19.7, 30.2, 35.0, 38.8, 48.1, 59.1, 92.5, 126.1, 128.3, 129.1, 136.5, 152.9, 169.5, 172.6; *m*/*z* (EI) 318 (M^+); HRMS (EI): M^+, found 318.1927. $C_{18}H_{26}N_2O_3$ requires 318.1943.

*4.4.5. 5-Ethyl 1-benzyl-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (**7d**).* Compound **7d** was obtained in 32% yield, accompanied by amide **8d** (48%) (Table 3, entry 5). *Compound* **7d**: Yellow oil; IR (neat) cm^{-1}: 2979, 1689, 1624, 1512, 1263, 1106; δ_H (600 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 4.17 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.24 (2H, s, C*H*$_2$Ph or 6-C*H*$_2$), 4.42 (2H, s, C*H*$_2$Ph or 6-C*H*$_2$), 7.22 (2H, d, *J* 8.4 Hz, Ar—*o*-*H*), 7.28—7.44 (6H, m, Ar—*H*), 7.49 (2H, dd, *J* 7.4, 1.5 Hz, Ar—*o*-*H*), 7.52 (1H, s, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 14.3, 45.9, 56.3, 60.0, 105.2, 127.1, 127.7, 128.0, 128.7, 129.0, 130.0, 134.8, 135.3, 145.8, 163.4, 166.1; *m*/*z* (EI) 320 (M^+); HRMS (EI): M^+, found 320.1502. $C_{20}H_{20}N_2O_2$ requires 320.1525.

*4.4.6. N-Benzyl-N-[(2-ethoxycarbonyl-3-methylamino)-prop-2-en-1-yl]benzamide (**8d**).* Colorless oil; IR (neat) cm^{-1}: 2933, 1673, 1644, 1631, 1100; δ_H (600 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 3.02 (3H, d, *J* 4.8 Hz, NHC*H*$_3$), 4.08 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.40 (2H, s, C*H*$_2$Ph or 6-C*H*$_2$), 4.57 (2H, s, C*H*$_2$Ph or 6-C*H*$_2$), 7.18 (2H, d, *J* 7.2 Hz, Ar—*o*-*H*), 7.29—7.41 (8H, m, Ar—*H*), 7.57 (1H, d, *J* 13.8 Hz, CH$_3$NHC*H*); δ_C (150 MHz, $CDCl_3$) 14.5, 35.2, 39.8, 52.3, 59.2, 92.7, 126.5, 126.9, 127.3, 128.47, 128.52, 129.6, 136.0, 137.1, 153.3, 169.7, 173.2; *m*/*z* (EI) 352 (M^+); HRMS (EI): M^+, found 352.1769. $C_{21}H_{24}N_2O_3$ requires 352.1787.

*4.4.7. 1-tert-Butyl 5-methyl 2-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (**7e**).* Yellow crystals; mp 115 °C (*n*-hexane); IR (KBr) cm^{-1}: 2994, 1722, 1533, 1369, 1288, 1149; δ_H (400 MHz, $CDCl_3$) 1.12 (9H, s, C*Me*$_3$), 3.82 (3H, s, OC*H*$_3$), 4.52 (2H, d, *J* 1.2 Hz, 6-C*H*$_2$), 7.41 (2H, t, *J* 7.2 Hz, Ar—*m*-*H*), 7.48 (1H, t, *J* 7.2 Hz, Ar—*p*-*H*), 7.65 (2H, d, *J* 7.2 Hz, Ar—*o*-*H*), 7.71 (1H, *J* 1.2 Hz, 4-C*H*); δ_C (100 MHz, $CDCl_3$) 27.4, 40.1, 51.9, 83.1, 115.3, 128.2, 128.5, 131.1, 136.7, 143.3, 151.9, 158.3, 165.2; *m*/*z* (EI) 316 (M^+); HRMS (EI): M^+, found 316.1410. $C_{17}H_{20}N_2O_4$ requires 316.1423.

*4.4.8. tert-Butyl 2-phenyl-5-phenylsulfonyl-1,6-dihydropyrimidine-1-carboxylate (**7f**).* Colorless crystals; mp 154—156 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 2973, 1727, 1601, 1524, 1313, 1146; δ_H (600 MHz, $CDCl_3$) 1.07 (9H, s, C*Me*$_3$), 4.40 (2H, d, *J* 1.2 Hz, 6-C*H*$_2$), 7.40 (2H, t, *J* 7.5 Hz, Ar—*m*-*H*), 7.49 (1H, t, *J* 7.5 Hz, Ar—*p*-*H*), 7.56 (2H, t, *J* 7.5 Hz, Ar—*m*-*H*), 7.60—7.67 (3H, m, Ar—*H*), 7.71 (1H, s, 4-C*H*), 7.94 (2H, d, *J* 7.5 Hz, Ar—*o*-*H*). δ_C (150 MHz, $CDCl_3$) 27.2, 39.5, 83.7, 123.7, 127.7, 128.3, 128.6, 129.4, 131.6, 133.6, 135.9, 139.8, 141.7, 151.3, 158.4; *m*/*z* (EI) 398 (M^+); HRMS (EI): M^+, found 398.1307. $C_{21}H_{22}N_2O_4S$ requires 398.1300.

*4.4.9. tert-Butyl 5-cyano-4-dimethylamino-2-phenyl-1,4,5,6-dihydropyrimidine-1-dicarboxylate (**7g**).* A solution of **3a** (100 mg, 0.365 mmol) and acrylonitrile (1.40 mL, 21.4 mmol) in mesitylene (0.7 mL) was heated at 100 °C for 13 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure to give cyclized products **6g** (29% NMR yield). The residue was dissolved in CH_2Cl_2 (3.7 mL) and MeI (0.230 mL, 3.69 mmol) was added to the solution dropwise at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 5 h, and triethylamine (1.8 mL), EtOAc (37 mL), water (37 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=60:30:1) to afford **7g** (21.6 mg, 0.0762 mmol, 21% for two steps) as pale yellow crystals; mp 156—157 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 2976, 2208, 1728, 1533, 1325, 1144; δ_H (400 MHz, $CDCl_3$) 1.14 (9H, s, C*Me*$_3$), 4.43 (2H, d, *J* 1.6 Hz, 6-C*H*$_2$), 7.41—7.45 (3H, m, Ar—*m*-*H* and 4-C*H*), 7.52 (1H, t, *J* 7.6 Hz, Ar—*p*-*H*), 7.64 (2H, d, *J* 8.0 Hz, Ar—*o*-*H*); δ_C (100 MHz, $CDCl_3$) 27.3, 40.5, 84.0, 95.9, 116.2, 128.4, 128.6, 131.7, 136.0, 147.5, 151.5, 158.4; *m*/*z* (EI) 283 (M^+); HRMS (EI): M^+, found 283.1296. $C_{16}H_{17}N_3O_2$ requires 283.1321.

4.5. General procedure for elimination of NMe_2 group of 6c and 6d using silica gel for synthesis of 7c and 7d

*4.5.1. Ethyl 1-butyl-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (**7c**).* Silica gel (510 mg, 1000 wt %) and molecular sieves 3 Å (25.5 mg, 50 wt %) was dried at heating in vacuo. To a mixture of the

silica gel and molecular sieves 3 Å was added a mixture of **6c** and **7c** (11.9:1.0, 51.0 mg, 0.155 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere. Stirring was continued at room temperature for 21 h. The reaction mixture was quenched with triethylamine (2 mL), filtered, and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/Et_3N=5:1) to afford **7c** (37.5 mg, 0.131 mmol, 84%) (See Experimental section 4.4.3).

*4.5.2. 5-Ethyl 1-benzyl-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (**7d**).* Similarly, compound **7d** was obtained from **6d** in 71% yield (See Experimental section 4.4.5).

4.6. General procedure for cyclization reaction of 1,3-diaza-1,3-butadiene 3a with olefins for synthesis of 7h and 7i

*4.6.1. tert-Butyl 5-benzoyl-2-phenyl-1,6-dihydropyrimidine-1-carboxylate (**7h**).* A solution of **3a** (161 mg, 0.585 mmol) and phenyl vinyl ketone (390 mg, 2.95 mmol) in mesitylene (2 mL) was heated at 100 °C for 13 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=60:4:1) to afford **7h** (196 mg, 0.541 mmol, 92%) as yellow crystals; mp 154–155 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 2966, 1714, 1626, 1523, 1373, 1097; δ_H (300 MHz, $CDCl_3$) 1.17 (9H, s, C*Me*$_3$), 4.71 (2H, d, *J* 1.2 Hz, 2-C*H*$_2$), 7.41–7.61 (7H, m, Ar–*H* and 6-C*H*), 7.66–7.75 (4H, m, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 27.3, 40.3, 83.2, 123.5, 128.2, 128.3, 128.5, 128.9, 131.2, 131.9, 136.5, 138.0, 146.6, 151.7, 158.4, 193.4; *m*/*z* (EI) 362 (M^+); HRMS (EI): M^+, found 362.1629. $C_{22}H_{22}N_2O_3$ requires 362.1630.

*4.6.2. tert-Butyl 5-(4-chlorobenzoyl)-2-phenyl-1,6-dihydropyrimidine-1-carboxylate (**7i**).* Yellow crystals; mp 122–123 °C (*n*-hexane/Et_2O); IR (KBr) cm^{-1}: 1705, 1631, 1524, 1369, 1331, 1147; δ_H (600 MHz, $CDCl_3$) 1.16 (9H, s, C*Me*$_3$), 4.69 (2H, s, 2-C*H*$_2$), 7.41–7.48 (5H, m, Ar–*H* and 6-C*H*), 7.51 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.65–7.72 (4H, m, Ar–*H*); δ_C (150 MHz, $CDCl_3$) 27.4, 40.3, 83.4, 123.4, 128.3, 128.6, 128.7, 130.4, 131.4, 136.3, 136.5, 138.3, 146.6, 151.8, 158.7, 192.1; *m*/*z* (EI) 396 (M^+); HRMS (EI): M^+, found 396.1247. $C_{22}H_{21}ClN_2O_3$ requires 396.1240.

4.7. General procedure for cleavage of *N*-Boc group from 7a, e–f, i for synthesis of 9a, e–f, i

*4.7.1. Ethyl 2-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (**9a**).* To a solution of **7a** (51.6 mg, 0.156 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.500 mL, 6.73 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and 2 M NaOH aqueous solution (10 mL) and EtOAc (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL×2). The combined organic layer was washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=50:25:1 to 25:25:1) to afford **9a** (34.9 mg, 0.152 mmol, 97%) as yellow crystals; mp 111–112 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 3165, 1702, 1682, 1668, 1504, 1262, 1100; δ_H (600 MHz, CD_3OD) 1.29 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.19 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.36 (2H, s, NC*H*$_2$), 7.33 (1H, s, NC*H*), 7.45 (2H, t, *J* 7.2 Hz, Ar–*m*-*H*), 7.52 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.69 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*); δ_C (150 MHz, CD_3OD) 14.7, 43.6, 61.2, 102.1, 128.0, 129.7, 132.4, 135.0, 141.4, 158.0, 167.8; *m*/*z* (EI) 230 (M^+); HRMS (EI): M^+, found 230.1069. $C_{13}H_{14}N_2O_2$ requires 230.1085.

*4.7.2. Methyl 2-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (**9e**).* Yellow crystals; mp 143–144 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 2947, 2850, 1695, 1508, 1263, 1107; δ_H (400 MHz, CD_3OD) 3.72 (3H, s, O*CH*$_3$), 4.36 (2H, s, NC*H*$_2$), 7.33 (1H, s, NC*H*), 7.45 (2H, t, *J* 7.2 Hz, Ar–*m*-*H*), 7.52 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.67 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*); δ_C (100 MHz, CD_3OD) 43.5, 51.8, 101.9, 128.0, 129.7, 132.4, 135.0, 141.5, 158.0, 168.2; *m*/*z* (EI) 216 (M^+); HRMS (EI): M^+, found 216.0902. $C_{12}H_{12}N_2O_2$ requires 216.0899.

*4.7.3. 2-Phenyl-5-phenylsulfonyl-1,4(6)-dihydropyrimidine (**9f**).* Colorless crystals; mp 200–202 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 2921, 1683, 1526, 1281, 1146; δ_H (600 MHz, CD_3OD) 4.24 (2H, s, 6-C*H*$_2$), 7.32 (1H, s, 4-C*H*), 7.43 (2H, t, *J* 7.5 Hz, Ar–*m*-*H*), 7.51 (1H, t, *J* 7.5 Hz, Ar–*p*-*H*), 7.62 (2H, t, *J* 7.5 Hz, Ar–*m*-*H*), 7.66 (2H, d, *J* 7.5 Hz, Ar–*o*-*H*), 7.69 (1H, t, *J* 7.5 Hz, Ar–*p*-*H*), 7.89 (2H, d, *J* 7.5 Hz, Ar–*o*-*H*); δ_C (150 MHz, CD_3OD) 43.4, 110.6 (br), 128.0, 128.4, 129.7, 130.5, 132.4, 134.5, 134.7, 139.4 (br), 141.5, 156.5 (br); *m*/*z* (EI) 298 (M^+); HRMS (EI): M^+, found 298.0786. $C_{16}H_{14}N_2O_2S$ requires 298.0776.

*4.7.4. p-Chlorophenyl 4-phenyl-2,3(5)-dihydropyrimidinyl ketone (**9i**).* Pale yellow crystals; mp 210–211 °C (*n*-hexane/chloroform); IR (KBr) cm^{-1}: 3336, 1673, 1584, 1554, 1476; δ_H (600 MHz, CD_3OD) 4.52 (2H, s, 6-C*H*$_2$), 7.10–7.26 (1H, br s, 4-C*H*), 7.48 (2H, t, *J* 7.2 Hz, Ar–*m*-*H*), 7.49 (2H, d, *J* 8.4 Hz, Ar–*H*), 7.55 (1H, t, *J* 7.2 Hz, Ar–*p*-*H*), 7.58 (2H, d, *J* 8.4 Hz, Ar–*H*), 7.74 (2H, d, *J* 7.2 Hz, Ar–*o*-*H*); *m*/*z* (EI) 296 (M^+); HRMS (EI): M^+, found 296.0682. $C_{17}H_{13}ClN_2O$ requires 296.0717.

4.8. Procedure for cleavage of *N*-Cbz and *N*-Bn groups (hydrogenation) from 7b and 7d

*4.8.1. Ethyl 2-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate (**9a**).* To a solution of **7b** (55.6 mg, 0.153 mmol) in EtOAc/MeOH (2:1, 3.0 mL) was added 10% Pd/C (11.0 mg, 20 wt %), and the reaction mixture was stirred at room temperature for 18 h under a hydrogen atmosphere (1 atm). The mixture was filtered through a Celite and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=60:30:1 to 50:50:1) to afford **9a** (31.1 mg, 0.135 mmol, 89%).

*4.8.2. Ethyl 3-benzyl-2-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**10**).* To a solution of **7d** (27.0 mg, 0.0843 mmol) in EtOAc/MeOH (2:1, 3 mL) was added 20% $Pd(OH)_2$/C (10.8 mg, 40 wt %), and the reaction mixture was stirred at room temperature for 4 h under a hydrogen atmosphere (1 atm). The mixture was filtered through a Celite and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=60:20:1 to 0:80:1) to afford **10** (8.90 mg, 0.0276 mmol, 33%) as a colorless oil; IR (neat) cm^{-1}: 3150–3480 (br), 1672, 1651, 1620, 1301, 1208, 1108; δ_H (600 MHz, DMSO-d_6) 1.12 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.92 (1H, d, *J* 15.9 Hz, PhC*H*), 3.12 (1H, d, *J* 15.9 Hz, PhC*H*), 3.57 (1H, d, *J* 13.5 Hz, 6-C*H*), 3.66 (1H, d, *J* 13.5 Hz, 6-C*H*), 3.95 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.94 (1H, d, *J* 3.0 Hz, 2-C*H*), 7.23–7.41 (10H, m, Ar–*H*), 7.59 (1H, dd, *J* 5.4, 3.0 Hz, 3-N*H*), 7.66 (1H, d, *J* 5.4 Hz, 4-C*H*); δ_C (150 MHz, $CDCl_3$) 14.5, 43.6, 57.0, 59.1, 70.3, 94.8, 126.8, 127.2, 128.0, 128.4, 128.5, 129.0, 138.9, 140.2, 140.9, 167.7; *m*/*z* (EI) 322 (M^+); HRMS (EI): M^+, found 322.1660. $C_{20}H_{22}N_2O_2$ requires 322.1681.

4.9. Three-step successive reactions from 3a for the synthesis of 9a

A solution of **3a** (208 mg, 0.757 mmol) and ethyl acrylate **5** (2.50 mL, 23.0 mmol) in mesitylene (6.0 mL) was heated at 100 °C for 13 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure to give cyclized products **6a**/**7a**. The residue was dissolved in CH_2Cl_2 (5.0 mL), and MeI

(0.470 mL, 7.55 mmol) was added to the solution dropwise at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 4 h, and quenched with triethylamine (2.0 mL), EtOAc (20 mL), water (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL×2). The combined organic layer was washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (8.0 mL) was added trifluoroacetic acid (2.00 mL, 26.9 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 5 h, and 2 M NaOH aqueous solution (20 mL) and EtOAc (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL×2). The combined organic layer was washed with water, brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the residue, which was purified by flash column chromatography (*n*-hexane/EtOAc/*i*-Pr_2NEt=80:40:1) to afford **9a** (105 mg, 0.456 mmol, 60%).

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Supplementary data

^1H and ^{13}C NMR spectra of all compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.064.

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