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Synthesis of 4-unsubstituted dihydropyrimidines having acyl and alkoxycarbonyl groups at 5- and 6-positions by cyclization–elimination reactions using 1,3-diaza-1,3-butadienes

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ABSTRACT

A synthetic method for novel 4-unsubstituted 2-phenyldihydropyrimidines having acyl and alkoxycarbonyl groups at the 5- and 6-positions was developed. The cyclization of 4-dimethylamino-1,3-diaza-1,3-butadiene having N-protecting groups (Boc, Cbz) with 1,2-disubstituted ethylenes, such as diethyl maleate, diethyl fumarate, (*Z*)-hex-3-ene-2,5-dione, (*E*)-1,4-diphenylbut-2-ene-1,4-dione, and unsymmetrical (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate, following the elimination of a dimethylamino group proceeded smoothly, producing the corresponding dihydropyrimidines in good overall yield. The N-protecting group (Boc) could be easily removed to obtain N-unsubstituted dihydropyrimidines as a mixture of tautomers, and their tautomeric behavior was analyzed by ^{1}H NMR spectroscopy.

Dihydropyrimidines have received much attention from synthetic and medicinal chemists due to their biological activities and unique physical and chemical characteristics.[1] They exhibit a wide range of activities for medicinal applications, such as antiviral, antitumor, antibacterial, and anti-inflammatory activities. In addition, they are regarded as calcium channel antagonists,[2] a ROCK1 inhibitor for cardiovascular diseases,[3] or a pharmaceutical agent for anti-hepatitis B virus replication.[4] Their anticancer potential has also been explored recently.[5] Therefore, the development of versatile synthetic methods for dihydropyrimidines and the expansion of the structural diversity of these compounds are important, and will contribute to medicinal chemistry.

The synthesis of dihydropyrimidines **1** has generally been performed by the reactions of (thio)urea **2** with aldehydes **3** and 1,3-dicarbonyl compounds **4**, or the reactions of amidines, guanidines, and *O*(*S*)-alkyliso(thio)urea derivatives **5** with α,β-unsaturated carbonyl compounds **6** (Scheme 1).[1a,6] Therefore, the R^1 and R^2 substituents at the C-4 and C-6 positions of **1** are typically alkyl or aryl groups, and the COR3 substituent at the C-5 position is an acyl, alkoxycarbonyl, or amide group. Multisubstituted dihydropyrimidines **1** are comparatively easy to synthesize, whereas less substituted dihydropyrimidines are difficult to prepare because of the difficulty in controlling the reactivity of formaldehyde (**3**; R^1 = H) or β-oxoaldehyde (**4**; R^2 = H) derivatives. To overcome this problem, during the course of our continuous research on dihydropyrimidines,[7] we previously developed the stepwise synthesis of 4,6-unsubstituted 2-phenyldihydropyrimidines having 5-substituents by using our designed protocol.[7d,e] It was a versatile method to obtain novel 2,5-disubstituted dihydropyrimidines.

On the other hand, as for the acyl, alkoxycarbonyl, or amide groups in dihydropyrimidines **1**, they have conventionally been located at the C-5 position. The groups could be introduced at the N-1 or N-3 position; in the case of carbonylation with dihydropyrimidine tautomers, it occurs predominantly at the N-3 position.[6f,7a,8] However, the introduction toward another position (especially the C-4 and C-6 positions) of the groups has scarcely been reported due to the lack of available synthetic methodologies.[9] Herein, we report a novel synthetic method using 1,3-diaza-1,3-butadienes **7** and 1,2-disubstituted ethylenes **8** to produce 4-unsubstituted dihydropyrimidines **9** having acyl and alkoxycarbonyl groups at the 5- and 6-positions (Scheme 2). Because dihydropyrimidines **9** are difficult to access by the conventional method described in Scheme 1, our results are significant and novel. The general formulae of **9** and deprotected N-unsubstituted dihydropyrimidines **10** shown in this Letter have not been reported in the literature. It should also be noted that we used a protocol simpler than the previous procedure,[7d,e] which was improved as a one-pot cyclization–elimination reaction sequence.

Our initial studies of the synthesis of dihydropyrimidines **9** started with the reaction between 1,3-diaza-1,3-butadiene **7a**[7e]

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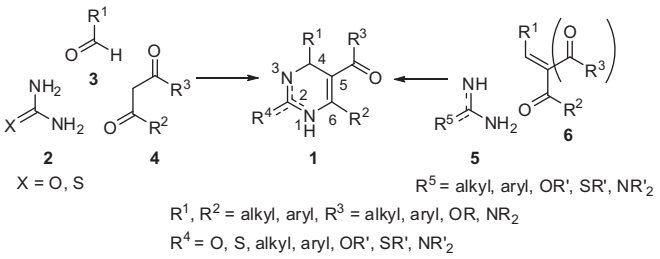
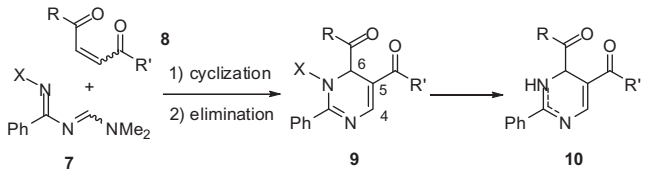


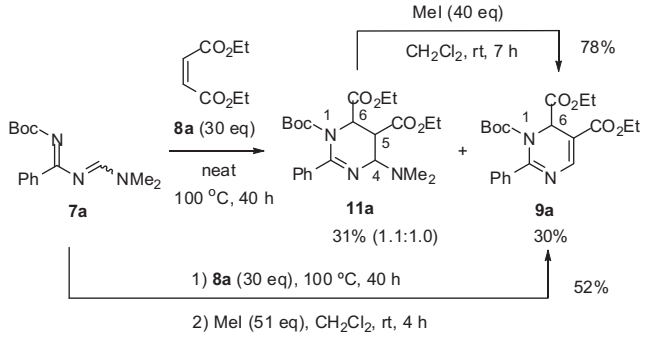
Scheme 1. Synthesis of dihydropyrimidines by condensation reactions.



Scheme 2. Synthetic strategy for dihydropyrimidines **9** and **10**.

and diethyl maleate **8a**. After the optimization of the reaction conditions, namely, the reaction temperature, the solvent used, and the molar ratio of the reactants, we found that the reaction proceeded smoothly with an excess amount of **8a** under solvent-free condition. Namely, **7a** reacted with **8a** (30 equiv) at 100 °C for 40 h to give three cyclized products; two stereoisomers of 1,4,5,6-tetrahydropyrimidine **11a** (1.1:1.0) and 1,6-dihydropyrimidine **9a** were obtained in 31% and 30% yields, respectively (Scheme 3). Successive elimination reaction of the 4-dimethylamino group of **11a** was attempted; when a mixture of two stereoisomers **11a** (1.1:1.0) was treated with MeI (40 equiv) in CH_2Cl_2 at room temperature for 7 h, **11a** underwent an elimination reaction to give **9a** in 78% yield (Scheme 3). For a more effective and operationally simple procedure, the one-pot synthesis of **9a** from **7a** was tested; the crude mixture after the cyclization of **7a** and **8a** was subjected to an elimination reaction [MeI (51 equiv) in CH_2Cl_2 for 4 h] to provide **9a** in 52% overall yield from **7a** (Scheme 3). The result indicates that the reaction of **11a** with MeI proceeded uneventfully without the isolation of **11a** from the crude mixture. Hence, we established the one-pot cyclization–elimination reaction sequence as the standard procedure in this study.

Next, the effect of an additive on the reaction was investigated to increase the yield of **9a**. Although none of the additives showed a crucial effect, the yield was slightly increased from 52% to 61% when the reaction was conducted in the presence of Li_2CO_3 (1.0 equiv) (Table 1, entry 1).[10] Other additives used such as Na_2CO_3, K_2CO_3, and BF_3 etherate did not show a superior effect. Under the optimized reaction conditions, various substrates were



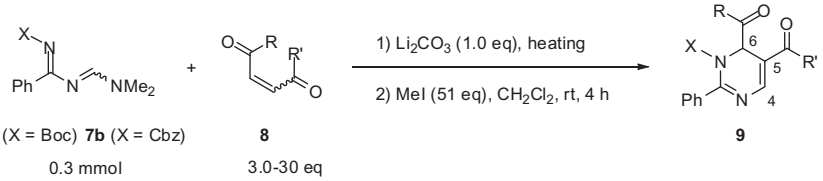
Scheme 3. Stepwise and one-pot synthesis of dihydropyrimidine **9a**.

subjected to sequential reactions to assemble dihydropyrimidines **9**, and the results are summarized in Table 1. In entry 2, diethyl fumarate **8b** showed a similar reactivity to **8a**, indicating that the olefin geometry of **8** did not affect the reactivity. Indeed, almost all of **8a** were isomerized and recovered as *trans* isomer **8b** at the end of the reaction (entry 1). In addition to ethyl ester **8a**, benzyl ester **8c**[11] could be applied to the reaction (entry 3). Benzyloxycarbonyl diazadiene **7b** also reacted with **8a**, producing **9c** in acceptable yield (entry 4). In the case of the diketone (*Z*)-hex-3-ene-2,5-dione **8d**,[12] it exhibited a higher reactivity than diesters **8a**–**c**. Therefore, the lower amount of **8d** (5.0 equiv) and the reaction temperature (80 °C) were sufficient to obtain **9d** in good yield (entry 5). Similarly, (*E*)-1,4-diphenylbut-2-ene-1,4-dione **8e** showed a higher reactivity to give **9e** in high yield (entry 6). The reaction of **7a** with *p*-tolyl derivative **8f**[13] was slower than that with unsubstituted **8e**, and provided **9f** in moderate yield (entry 7). Even with unsymmetrical (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate **8g**, the reaction proceeded smoothly to give two dihydropyrimidines in 72% yield (entry 8); 6-ethoxycarbonyl 5-benzoyl dihydropyrimidine **9g** (62%) and 5-ethoxycarbonyl 6-benzoyl derivative **9h** (10%) were isolated. The structure of the major compound **9g** was assigned by NOE experiments: a significant NOE (1.3%) was observed between the 4-H vinyl proton (δ 7.38) and the aromatic protons (δ 7.80) of the 5-benzoyl group. Therefore, its structure was determined to be **9g**. Thus, the N–C bond formation between **7a** and **8g** occurred preferentially at the β-position of the benzoyl group of **8g** due to the stronger electron withdrawing property of the ketone than of the ester. Unfortunately, our attempt to react **7a** with other 1,2-disubstituted ethylenes such as ethyl cinnamate, chalcone, 2-cyclohexen-1-one, maleimide, and fumaric anhydride failed under our reaction conditions; only the decomposition or recovery of the starting materials occurred without the detection of cyclized products.

Finally, the N-protecting (Boc) group was removed and N-unsubstituted dihydropyrimidines **10** were synthesized (Table 2). Compound **9a** was treated with excess trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature to afford **10a** in 95% yield (entry 1).[14] The deprotection reaction of **9g** with TFA proceeded to give **10g** in high yield (entry 2). Subsequently, the tautomeric behavior of **10a** and **10g** was analyzed by ^{1}H NMR spectroscopy. The spectra were measured in CD_3OD, $CDCl_3$, and DMSO-d_6 at 25 °C (0.01 M, 600 MHz). Prior to the analysis, $CDCl_3$ was filtered through activated aluminum oxide in order to eliminate the effect of trace amounts of acid on tautomerization. Diester **10a** was observed as two independent isomers at ratios of 1.6:1.0 ($CDCl_3$) and 4.9:1.0 (DMSO-d_6) (entry 1). The observed signals of NH protons [δ 9.94 (major), δ 9.22 (minor)] and 4-protons [δ 5.16 (major), δ 5.01 (minor)] in DMSO-d_6 indicated that the two isomers were 1,4- and 1,6-tautomers. The major tautomer of **10a** in DMSO-d_6 was assigned to the 1,4-isomer because the 6-H vinyl proton (δ 7.31) was observed as a doublet peak by its coupling (J = 5.4 Hz) with the 1-NH proton (δ 9.94). In CD_3OD, **10a** was observed as a single isomer (average spectrum of tautomers). As for **10g**, two tautomers were observed only in $CDCl_3$ (entry 2). The major tautomer of **10g** in $CDCl_3$ was assigned to the 1,6-isomer because the 6-H proton (δ 5.60) was observed as a doublet peak by its coupling (J = 2.4 Hz) with the 1-NH proton. In our previous report, 2-phenyldihydropyrimidine 5-carboxylic acid ethyl ester showed a similar behavior to **10a**; the 1,4-isomer was observed as a major tautomer in DMSO-d_6.[7e] These analytical results showed that the position and property of acyl and alkoxycarbonyl groups in dihydropyrimidines significantly affected the rate of hydrogen transfer in tautomerism.

In summary, it was demonstrated that 4-unsubstituted 2-phenyldihydropyrimidines having acyl and alkoxycarbonyl groups at the 5- and 6-positions were synthesized by the cyclization-elimination reaction sequence. The reactions using 1,2-disubstituted

Table 1
Synthesis of dihydropyrimidines **9**

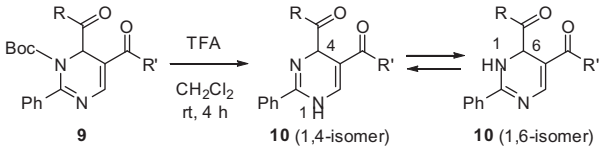


7a (X = Boc) **7b** (X = Cbz) 0.3 mmol — **8** 3.0-30 eq — **9**

Entry	Diene **7**	Substrate **8**	Reaction conditions	Product **9**	Yield[a] (%)
1	**7a**	**8a** (R = Et, *cis* isomer, 30 equiv)	100 °C, 40 h	**9a** (R = Et)	61
2	**7a**	**8b** (R = Et, *trans* isomer, 30 equiv)	100 °C, 40 h	**9a** (R = Et)	61
3	**7a**	**8c** (R = Bn, *cis:trans* = 5.0:1.0, 30 equiv)	100 °C, 18 h	**9b** (R = Bn)	52
4	**7b**	**8a** (R = Et, *cis* isomer, 30 equiv)	100 °C, 60 h	**9c**	50
5[b]	**7a**	**8d** (R = CH_3, *cis* isomer, 5.0 equiv)	80 °C, 12 h	**9d** (R = CH_3)	64
6[b]	**7a**	**8e** (R = Ph, *trans* isomer, 3.0 equiv)	80 °C, 15 h	**9e** (R = Ph)	77
7[c]	**7a**	**8f** (R = C_6H_4*p*-Me, *trans* isomer, 5.0 equiv)	80 °C, 40 h	**9f** (R = C_6H_4*p*-Me)	56
8[b]	**7a**	**8g** (5.0 equiv)	80 °C, 48 h	**9g** + **9h** (**9g**:**9h** = 6.2:1.0)	72

[a] Overall yield of **9** from **7** (two steps).
[b] Mesitylene (0.5 mL) was used as solvent.
[c] Mesitylene (1.0 mL) was used as solvent.

Table 2
Synthesis and ^{1}H NMR analysis of N-unsubstituted dihydropyrimidines **10a** and **10g**



9 — **10** (1,4-isomer) — **10** (1,6-isomer)

Entry	Product **10**	Yield (%)	CD_3OD	$CDCl_3$	DMSO-d_6
1	**10a**	95	Single	1.6:1.0	4.9:1.0
2	**10g**	95	Single	1.0:1.6	Single

ethylenes, such as diethyl maleate, diethyl fumarate, (*Z*)-hex-3-ene-2,5-dione, (*E*)-1,4-diphenylbut-2-ene-1,4-dione, and unsymmetrical (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate, proceeded smoothly to give the corresponding dihydropyrimidines. Because all the dihydropyrimidines presented in this Letter have hitherto been unavailable compounds, this unprecedented achievement should contribute largely to the expansion of dihydropyrimidine-based heterocyclic chemistry and pharmaceutical sciences for drug development.

Supplementary data

Supplementary data (synthesis and characterization of compounds, spectroscopic data of IR, NMR, MS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.038.

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10. Under an atmosphere of argon, a mixture of **7a** (82.5 mg, 0.300 mmol), **8a** (1.45 mL, 9.00 mmol), and Li_2CO_3 (22.0 mg, 0.300 mmol) was heated at 100 °C for 40 h. After cooled to room temperature, the reaction mixture was filtrated and concentrated under reduced pressure. To the crude mixture was added CH_2Cl_2 (2.0 mL) and MeI (0.950 mL, 15.3 mmol) at 0 °C and the mixture was stirred at room temperature for 4 h. After removal of excess MeI under reduced pressure, to the reaction mixture was added EtOAc (15 mL) followed by saturated $NaHCO_3$ aqueous solution (5 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (15 mL), and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography [hexane–EtOAc–$(i\text{-Pr})_2$NEt (40:5:1)] to give **9a** (73.2 mg, 0.182 mmol, 61%) as colorless crystals. mp 97–98 °C (hexane). IR (KBr) cm^{-1}: 2980, 1745, 1726, 1534, 1369, 1285, 1223, 1151. ^{1}H NMR ($CDCl_3$) δ 1.13 (9H, s), 1.23 (3H, t, J = 7.2 Hz), 1.36 (3H, t, J = 7.2 Hz), 4.14 (1H, dq, J = 10.8, 7.2 Hz), 4.20 (1H, dq, J = 10.8, 7.2 Hz), 4.29 (1H, dq, J = 10.8, 7.2 Hz), 4.37 (1H, dq, J = 10.8, 7.2 Hz), 5.99 (1H, s), 7.43 (2H, t, J = 7.8 Hz), 7.49 (1H, t, J = 7.8 Hz), 7.73 (1H, s), 7.84 (2H, d, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 14.3, 27.3, 51.2, 60.9, 62.0, 83.8, 114.9, 128.1, 128.6, 131.0, 136.7, 142.3, 151.5, 156.9, 164.6, 169.0. HRMS-FAB m/z: 403.1863 (Calcd for $C_{21}H_{27}N_2O_6$: 403.1869). MS (FAB) m/z: 403 [$(M+H)^+$].
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14. To a solution of **9a** (111 mg, 0.276 mmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (0.800 mL, 10.8 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 at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography [hexane-EtOAc-Et_3N (30:20:1)] to give **10a** (79.5 mg, 0.263 mmol, 95%) as a yellow oil. IR (neat) cm^{-1}: 2982, 1739, 1698, 1478, 1254, 1196. ^{1}H NMR (CD_3OD) δ 1.27 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 4.15–4.27 (4H, m), 5.24 (1H, s), 7.38–7.60 (4H, m), 7.65–7.85 (2H, m). ^{13}C NMR (CD_3OD) δ 14.5, 14.6, 57.2, 61.5, 62.5, 101.8, 128.3, 129.7, 132.6, 134.7, 139.7, 156.5, 167.5, 172.9. HRMS-FAB m/z: 303.1334 (Calcd for $C_{16}H_{19}N_2O_6$: 303.1345). MS (FAB) m/z: 303 [$(M+H)^+$].