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Convergent synthesis of 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines by substitution reactions of Weinreb amide group of tetrahydropyrimidines

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Organolithium reagent

ABSTRACT

A method of convergent and stepwise synthesis of novel 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines using the Weinreb amide group is developed. The cyclization of 4-dimethylamino-1,3-diaza-1,3-butadiene having N-protecting groups (Boc) with *N*-methoxy-*N*-methylacrylamide gives 6-unsubstituted 4-dimethylamino-2-phenyltetrahydropyrimidine, which is a synthetic intermediate for 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines. The transformation of the Weinreb amide group to an acyl group via substitution reaction using organolithium reagents, following the elimination of a dimethylamino group using MeI proceeds smoothly, affording 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines in good overall yield. The N-protecting group can be easily removed to obtain N-unsubstituted dihydropyrimidines as a mixture of tautomers, and their tautomeric behaviors were analyzed by ^{1}H NMR spectroscopy.

Dihydropyrimidines have received much attention from synthetic and medicinal chemists owing 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.

Dihydropyrimidines **1** have generally been synthesized 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 COR^3 substituent at the 5-position is an acyl, alkoxycarbonyl, or amide group. Multisubstituted dihydropyrimidines **1** are comparatively easy to synthesize, whereas the synthesis of less substituted dihydropyrimidines is problematic. Some reasons for this problem are as follows: it is difficult to control the high reactivity of formaldehyde (**3**; R^1 = H), and β-oxoaldehyde (**4**; R^2 = H) is not easily available in the multicomponent reactions described above. To overcome these difficulties during the course of our continuous research on dihydropyrimidines,[7] we previously developed a method of stepwise synthesis of 4,6-unsubstituted 2-phenyldihydropyrimidines **7** having various 5-substituents via the cyclization of 1,3-diaza-1,3-butadiene **8** and electron-deficient olefins **9** (Scheme 2).[7d–f] It was a versatile method to obtain novel 4,6-unsubstituted dihydropyrimidines **7**. Although this method is useful for the synthesis of some 5-acyl-2-phenyldihydropyrimidine derivatives, the olefin substrates having ketones such as benzoyl or 4-chlorobenzoyl groups are not commercially available and need to be prepared.[7d,e] In addition, alkyl vinyl ketones such as methyl vinyl ketone were not applicable. These problems led us to explore a more efficient route for synthesizing 5-acyl-2-phenyldihydropyrimidines.

In this study, we utilized the Weinreb amide group (*N*-methoxy-*N*-methyl amide group) as an acyl group precursor. The Weinreb amide group is a versatile and reliable functional group that is easily converted to an acyl group via nucleophilic substitution reaction using Grignard or organolithium reagents.[8] Herein, we

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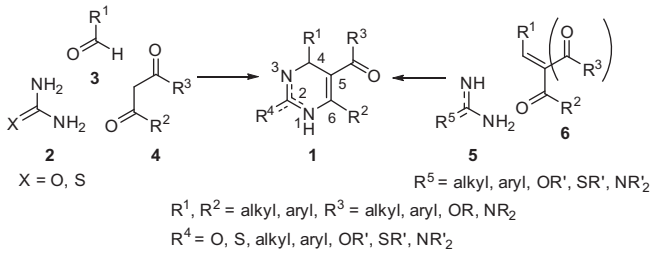
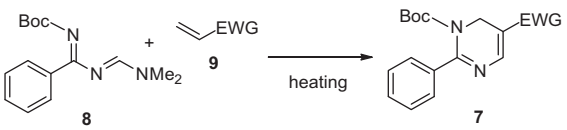


Scheme 1. Synthesis of dihydropyrimidines by condensation reactions.

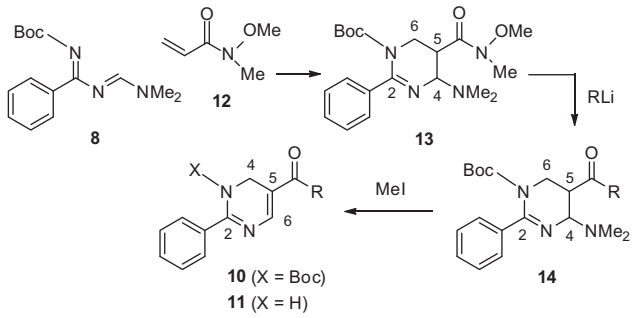
describe a convergent synthesis of 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines **10** and **11** from 1,3-diaza-1,3-butadiene **8** and *N*-methoxy-*N*-methylacrylamide **12** (Scheme 3). Namely, the cyclization of **8** and **12** provides 6-unsubstituted 4-dimethylamino-2-phenyltetrahydropyrimidine **13** having the Weinreb amide at 5-position. Subsequently, the substitution reaction of the Weinreb amide group of **13** with organolithium reagents gives 6-unsubstituted 5-acyl-4-dimethylamino-2-phenyltetrahydropyrimidine **14**, and the subsequent elimination reaction of the 4-dimethylamino group of **14** with MeI affords **10**. The synthesis of dihydropyrimidine **10** is difficult by conventional methods. In fact, to the best of our knowledge, the general formulae of **10** and N-unsubstituted dihydropyrimidines **11** shown in this paper have not been reported in the literature.

First, we prepared dihydropyrimidines and related derivatives having the Weinreb amide. *N*-methoxy-*N*-methylacrylamide **12** was synthesized from acryloyl chloride and *N*-methoxy-*N*-methylamine hydrochloride under basic condition, and the reaction of **12** with 1,3-diaza-1,3-butadiene **8**[9] was investigated (Scheme 4). Unlike the optimized reaction conditions in our previous studies,[7d–f] the use of large excess amount (30 equiv) of **12** or solvent-free condition resulted in a low yield of the cyclized product tetrahydropyrimidine **13**, because of polymerization of **12**. We eventually found that the reaction proceeded smoothly using **12** (10 equiv) in mesitylene (0.6 M) in the presence of Li_2CO_3 (1.0 equiv) at 100 °C for 48 h to give **13** in 71% yield as a single stereoisomer. The relative configuration of **13** was determined to be *anti* between 4-position and 5-position using NOE experiments (see; Supplementary Material). Successive elimination reactions of **13** gave **15** in 74% yield (Scheme 4). The N-protecting group (Boc) of **15** was removed and N-unsubstituted dihydropyrimidine **16** was synthesized; **15** was treated with excess trifluoroacetic acid (TFA) to afford **16** in 89% yield. Therefore, dihydropyrimidines **15** and **16** could be obtained as substrates for the synthesis of 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines.

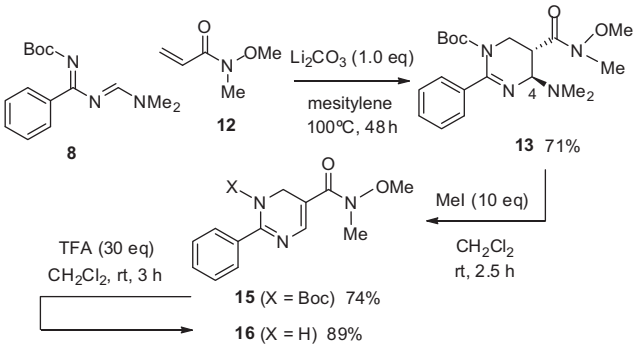
Having secured **15** and **16** in hand, the substitution reactions of the Weinreb amide group of **15** with nucleophilic reagents were investigated (Scheme 5). The reaction of **15** with methylmagnesium bromide in THF proceeded smoothly to give the 5-acetyl derivative **10a** in 82% yield. However, the reactions with other Grignard reagents such as *n*-butylmagnesium chloride or phenylmagnesium bromide gave a complex mixture to afford the 5-acyl products **10b** or **10c** in low yields even though the starting material **15** was consumed. Taking into account of the side reactions



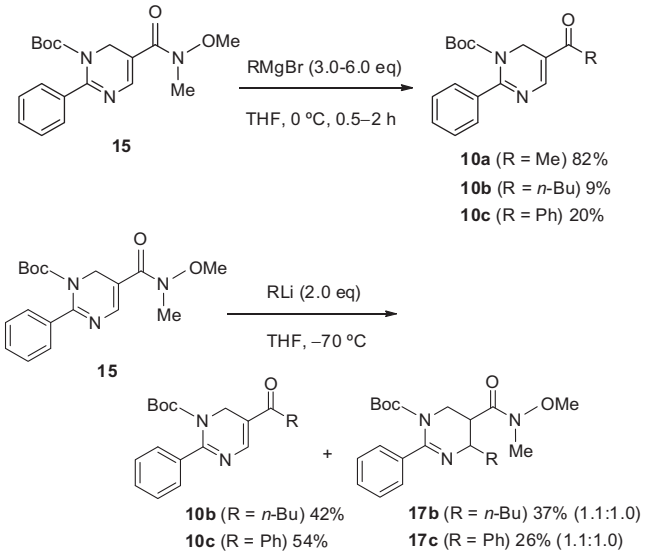
Scheme 2. Synthesis of 4,6-unsubstituted 2-phenyldihydropyrimidines **7** from 1,3-diaza-1,3-butadiene **8**.



Scheme 3. Synthetic strategy for 5-acyl-2-phenyldihydropyrimidines **10** and **11**.



Scheme 4. Synthesis of tetrahydropyrimidine **13** and dihydropyrimidines having Weinreb amide group **15** and **16**.



Scheme 5. Reactions of dihydropyrimidine **15** with Grignard or organolithium reagents.

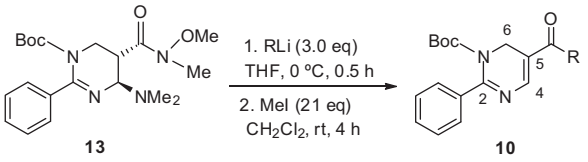
with the Boc group of **15** with Grignard reagents, N-unsubstituted dihydropyrimidine **16** was used as an alternative substrate. However, the reactions of **16** also gave similar results giving low yields of the 5-acyl product. Next, we tested the use of organolithium reagents in the reaction with **15** instead of Grignard reagents. Both reactions using *n*-butyllithium or phenyllithium gave the corresponding 5-acyl derivatives **10** in moderate yields (42% or 54%) with considerable amounts of side products **17** as a mixture of stereoisomers (1.1:1.0) derived from the conjugate addition of organolithium reagents to **15**.

To prevent the production of **17** in the reaction using organolithium reagents, the substrate was changed from dihydropyrimidines to tetrahydropyrimidine **13**. When **13** was reacted with butyllithium (3.0 equiv) in THF at 0 °C, the desired 5-pentanoyl tetrahydropyrimidine **14b** (R = *n*-Bu) was obtained in a quantitative yield without detection of any byproduct (Table 1, entry 1). When less amount of butyllithium (1.5–2.0 equiv) than 3.0 equiv was used in the reaction with **13**, **14b** was obtained but the reaction was not completed by TLC analysis. Therefore, 3.0 equiv of butyllithium was needed for complete consumption of **13**. It is probably due to the coordination of three nitrogen atoms of 4-dimethylaminotetrahydropyrimidines **13** to deactivate organolithium reagents. Because **14b** was unstable during purification by silica gel column chromatography, the crude product was treated with MeI to obtain **10b** in 85% isolated yield in two steps from **13** (Table 1, entry 1).[10] The reactivity of methylmagnesium bromide with **13** was also tested. However, the reaction was slow even at 40 °C for 41 h, and 5-acetyl tetrahydropyrimidine was produced in only 12% yield. Thus, it was found that the use of tetrahydropyrimidine **13** as a substrate and organolithiums as alkylating reagents gives **10** in high yield. Under the optimized reaction conditions, various substrates were subjected to sequential reactions to form 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines **10**, and the results are summarized in Table 1. The reaction using phenyllithium proceeded smoothly to afford the 5-benzoyl product **10c** in 89% yield in two steps (entry 2). In entry 3, (phenylethynyl) lithium also exhibited good reactivity, affording **10d** in 86% yield. Various aryllithiums, prepared in situ from corresponding aryl bromide and *t*-butyllithium, reacted smoothly with **13** to give 5-aryloyl dihydropyrimidines **10e–h** in good yields (entries 4–7). In the case of entry 8, the reaction using heterocyclic 2-lithiated thiophene afforded 5-(2-thiophenecarbonyl)dihydropyrimidine **10i** in 65% yield.

The synthesis of hitherto unavailable 5-formyl dihydropyrimidine **18** was examined (Scheme 6). When **13** was reacted with diisobutylaluminum hydride (DIBAL-H) and MeI, two-step reactions proceeded smoothly to give 5-formyl dihydropyrimidine **18** in 68% yield. Further transformation of the 5-formyl group of **18** was attempted; the Horner–Emmons reaction using triethyl phosphonoacetate and sodium hydride afforded novel dihydropyrimidine **19** having the conjugated ester group at 5-position in a high yield of 93%.

The N-protecting group (Boc) was removed and N-unsubstituted dihydropyrimidines **11** were synthesized (Table 2). **10b** was treated with excess TFA in CH_2Cl_2 at room temperature to afford **11b** in 91% yield (entry 1).[11] The deprotection reactions of **10c–j** with TFA also proceeded to give **11c–j** in high yields, respectively (entries 2–7). Subsequently, the tautomeric behaviors of **11b–j** were analyzed by ^{1}H NMR spectroscopy. The spectra were measured in CD_3OD and DMSO-d_6 at 25 °C (0.01 M, 600 MHz). While all dihydropyrimidines **11** were observed as a single isomer (average spectrum of tautomers) in CD_3OD, **11g** and **11j** were observed as two independent isomers at ratios of 1.3:1.0 and 1.5:1.0 in DMSO-d_6, respectively (entries 5 and 7). In the ^{1}H NMR spectrum of **11g** in DMSO-d_6, the observed signals of NH protons [δ 9.75 (major), δ 9.00 (minor)] and 4-protons [δ 4.51 (major), δ 4.38 (minor)] indicated that thetwo isomers were 1,4- and 1,6-tautomers. The major tautomer of **11g** in DMSO-d_6 was assigned to the 1,4-isomer because the 6-H vinyl proton (δ 6.94) was observed as a doublet peak by its coupling (J = 4.2 Hz) with the 1-NH proton (δ 9.75). In the ^{1}H NMR spectrum of **11j** in DMSO-d_6, the major tautomer of **11j** was assigned to the 1,4-isomer because the 6-H vinyl proton (δ 6.96) was observed as a doublet peak by its coupling (J = 4.2 Hz) with the 1-NH proton (δ 9.72). Therefore, 5-aryloyl-2-phenyldihydropyrimidines having electron-withdrawing moieties, such as trifluoromethyl or chloro groups at *para*-position, showed relatively low rates of hydrogen transfer in tautomerism. In our previous report, 2-phenyldihydropyrimidines having 5-carboxylic acid ethyl ester or 5-phenylsulfonyl groups also showed similar behaviors to **11g** and **11j**; the 1,4-isomers were observed as major tautomers in DMSO-d_6.[7e] These analytical results showed that the property of 5-substituents in dihydropyrimidines affected the rate of hydrogen transfer in tautomerism and the stability of each tautomer.

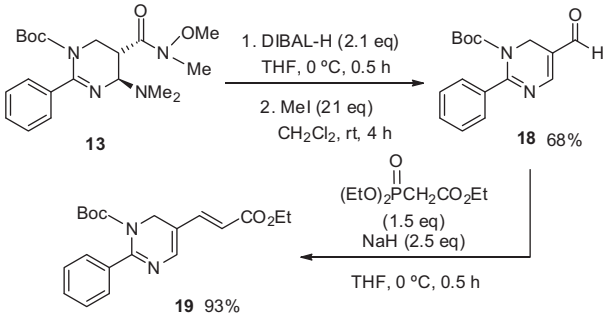
Table 1
Synthesis of 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines **10**



13 10

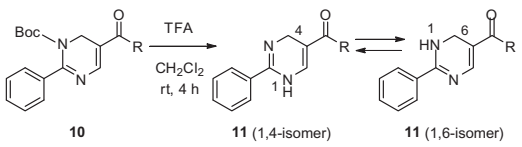
Entry	R	10	Yield %[a]
1[b]	*n*-Bu	**10b**	85
2	Ph	**10c**	89
3	Phenylethynyl	**10d**	86
4	4-MeC_6H_4	**10e**	80
5	4-MeOC_6H_4	**10f**	79
6	4-$CF_3C_6H_4$	**10g**	76
7	2-Naphthyl	**10h**	76
8	2-Thienyl	**10i**	65

[a] Yield in two steps from **13**.
[b] Reaction time was 1 h.



Scheme 6. Synthesis of 4,6-unsubstituted 5-formyl-2-phenyldihydropyrimidine **18** and Horner–Emmons reaction.

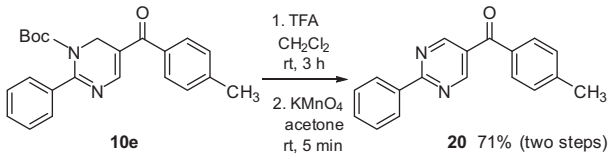
Table 2
Synthesis and ^{1}H NMR analysis of N-unsubstituted dihydropyrimidines **11**



10 11 (1,4-isomer) 11 (1,6-isomer)

Entry	R	11	Yield %	Ratio of 1,4-/1,6-tautomers **11**	
				CD_3OD	DMSO-d_6
1	*n*-Bu	**11b**	91	Single	Single
2	Ph	**11c**	91	Single	Single
3	4-MeC_6H_4	**11e**	96	Single	Single
4	4-MeOC_6H_4	**11f**	95	Single	Single
5	4-$CF_3C_6H_4$	**11g**	100	Single	1.3:1.0
6	2-naphthyl	**11h**	98	Single	Single
7[a]	4-ClC_6H_4	**11i**	100	Single	1.5:1.0

[a] Ref. 7e.



Scheme 7. Synthesis of 5-(4-methylbenzoyl)-2-phenylpyrimidine **20**.

The transformation of a dihydropyrimidine to its corresponding pyrimidine derivative was also examined. Namely, N-unsubstituted dihydropyrimidine **11e** was synthesized by the deprotection of **10e** under acidic condition, and oxidized using $KMnO_4$ to give 2-phenyl-5-(4-methylphenyl)pyrimidine **20** in 71% yield after recrystallization in two steps (Scheme 7). This method is useful for the synthesis of novel 2-phenyl-5-aryloylpyrimidine derivatives because the pyrimidines have not been reported in the literature.

In summary, it was demonstrated that 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines **10** and **11** were synthesized using the Weinreb amide group as an acyl precursor. The combination of tetrahydropyrimidine **13** as a substrate and organolithiums as alkylating reagents is significant for the effective nucleophilic substitution reaction of the Weinreb amide group. Given that dihydropyrimidines **10** and **11** were previously unavailable and difficult to synthesize, the achievement in this study should contribute largely to the expansion of dihydropyrimidine-based heterocyclic chemistry and pharmaceutical sciences for drug development.

Acknowledgment

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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.2016.08.077.

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9. Preparation of 1,3-diaza-1,3-butadiene 8; see Ref. 7e.
10. Under an atmosphere of argon, to a solution of **13** (39.0 mg, 0.100 mmol) in THF (0.5 mL) was added butyllithium (1.6 M in hexane, 0.13 mL, 0.208 mmol) dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 0.5 h. For complete consumption of **13**, further butyllithium (1.6 M in hexane, 0.06 mL, 0.096 mmol) was added, and the reaction mixture was stirred at 0 °C for 0.5 h. To the reaction mixture was added saturated NH_4Cl aqueous solution (5 mL) followed by 1 M NaOH solution (8 mL) at 0 °C, and EtOAc (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (15 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. To the crude mixture in CH_2Cl_2 (1.0 mL) was added MeI (0.130 mL, 2.09 mmol) at room temperature 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 (20 mL) followed by 1 M NaOH aqueous solution (10 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL × 2), and 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 (200:20:1 to 100:20:1)] to give **10b** (29.2 mg, 0.0853 mmol, 85%) as a yellow oil.
11. To a solution of **10b** (42.8 mg, 0.125 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.370 mL, 4.98 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and 2 M NaOH aqueous solution (7.5 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 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 [CH_2Cl_2-EtOAc-Et_3N (50:50:1)] to give **11b** (27.5 mg, 0.113 mmol, 91%) as a yellow solid.