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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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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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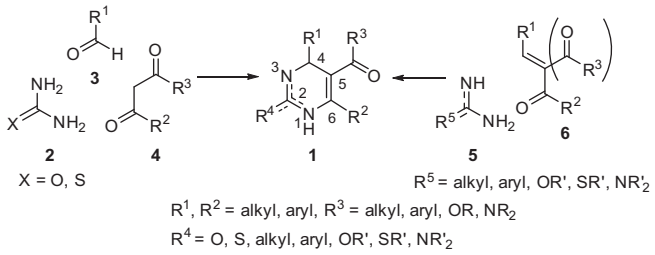
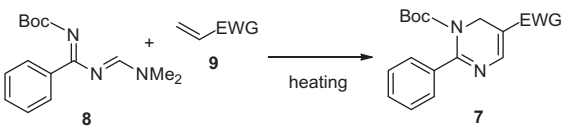


Scheme 1. Synthesis of dihydropyrimidines by condensation reactions.

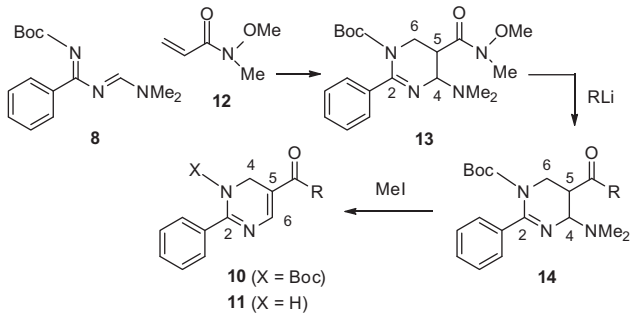
describe a convergent synthesis of 4,6-unsubstituted 5-acyl-2-phenyldihydropyrimidines **10** and **11** from 1,3-diaza-1,3-butadiene **8** and *N*-methoxy-*N*-methylacrylamide **12** (Scheme 3). Namely, the cyclization of **8** and **12** provides 6-unsubstituted 4-dimethylamino-2-phenyltetrahydropyrimidine **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.

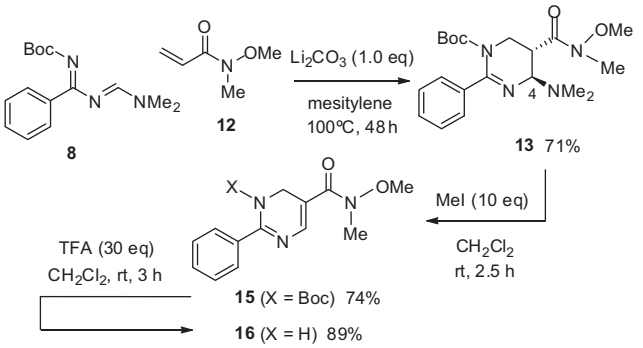
Having secured **15** and **16** in hand, the substitution reactions of the Weinreb amide group of **15** with nucleophilic reagents were investigated (Scheme 5). The reaction of **15** with methylmagnesium bromide in THF proceeded smoothly to give the 5-acetyl derivative **10a** in 82% yield. However, 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



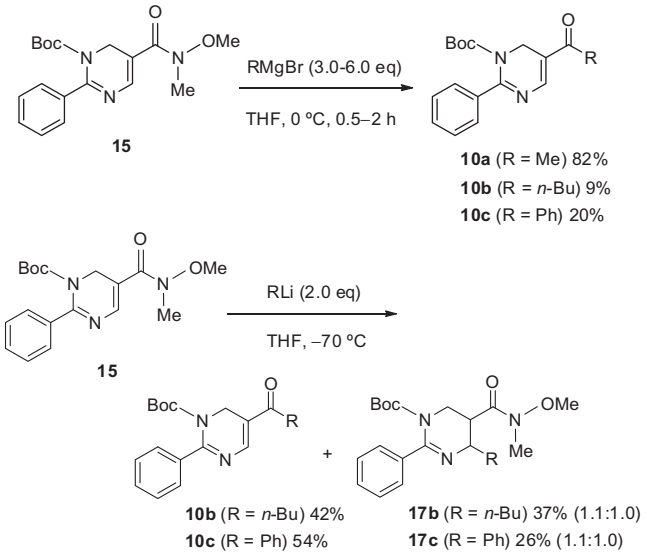
Scheme 2. Synthesis of 4,6-unsubstituted 2-phenyldihydropyrimidines **7** from 1,3-diaza-1,3-butadiene **8**.



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**.