Synlett Y. Nishimura, H. Cho Letter

Synthesis of 4,6-Unsubstituted 2-Aminodihydropyrimidine-5-carboxylates through Sequential Staudinger/Aza-Wittig/Cyclization Reactions

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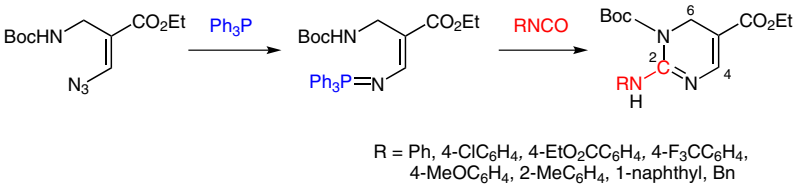


R = Ph, 4-ClC$_6$H$_4$, 4-EtO$_2$CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 1-naphthyl, Bn

Received: 18.09.2014
Accepted after revision: 16.10.2014
Published online: 18.11.2014
DOI: 10.1055/s-0034-1378932; Art ID: st-2014-u0779-l

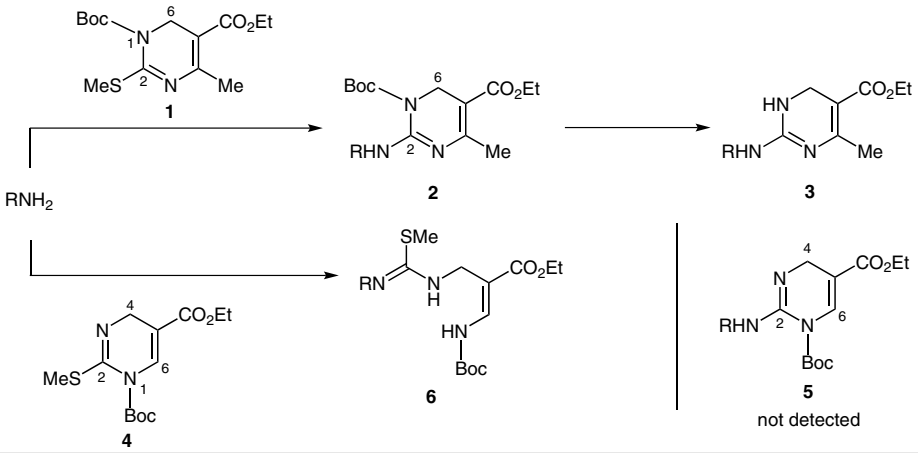
Abstract A novel method for constructing the dihydropyrimidine skeleton is developed. The method involves three sequential reactions: (1) the Staudinger reaction of (*E*)-ethyl 3-azido-2-{[(*tert*-butoxycarbonyl)amino]methyl}acrylate with triphenylphosphine; (2) aza-Wittig reaction of the resulting iminophosphorane with isocyanate; (3) intramolecular cyclization of the carbodiimide intermediate to give 4,6-unsubstituted 2-aminodihydropyrimidine-5-carboxylates in high overall yield. The method can be applied to various aromatic isocyanates, with substrates having electron-withdrawing groups showing high reactivities. In the case of aliphatic benzyl isocyanate, the reaction provides bicyclic dihydropyrimidine as the major product. The N-protecting group (Boc) can easily be removed to obtain N-unsubstituted dihydropyrimidines. All dihydropyrimidines in this study were previously unavailable and are difficult to synthesize by conventional methods.

Key words dihydropyrimidine, heterocycles, Staudinger reaction, aza-Wittig reaction, cyclization

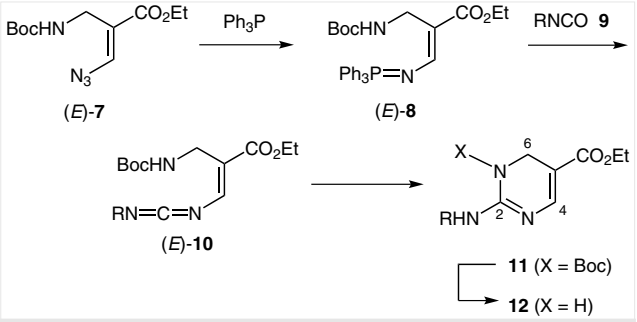
Dihydropyrimidines have received much attention from synthetic and medicinal chemists because of their biological activities as well as their physical and chemical characteristics.[1] They exhibit a wide range of biological activities including antiviral, antitumor, antibacterial, and anti-inflammatory properties.[1] They are also regarded as pharmaceutical agents serving as calcium channel antagonists,[2] Ca^{2+}-ATPase inhibitors,[3] and ROCK1 inhibitors for cardiovascular diseases[4] or anti-hepatitis B virus replication.[5] Their anticancer potential has recently been explored.[6] Therefore, the development of novel methods of synthesizing dihydropyrimidines and the expansion of their structural diversity is expected to contribute significantly to medicinal chemistry.

Dihydropyrimidines have conventionally been synthesized by either the three-component condensation of (thio)urea, aldehydes (RCHO), and 1,3-dicarbonyl compounds or by the two-component cyclization of amidines, guanidines, or *O*(*S*)-alkyliso(thio)urea with enone derivatives prepared from aldehydes and 1,3-dicarbonyl compounds.[1] Generally, these methods give multisubstituted dihydropyrimidines with alkyl or aryl groups at the C-4 and C-6 positions, and an acyl, alkoxycarbonyl, or amide group at the C-5 position. Whereas other methods for the synthesis of such multisubstituted derivatives have been reported,[7] less substituted dihydropyrimidines are comparatively difficult to synthesize. To overcome this problem, during the course of our research on the synthesis of less substituted dihydropyrimidines,[8] we previously reported the synthesis of 4,6- or 4-unsubstituted 2-phenyldihydropyrimidines by a novel [4+2] cyclization of 1,3-diaza-1,3-butadienes with olefins.[8a–c] We also developed a nucleophilic substitution reaction of N1-protected 6-unsubstituted 2-methylthiodihydropyrimidine **1** with amines as another approach for synthesizing 6-unsubstituted 2-aminodihydropyrimidines **2** and N-unsubstituted products **3** (Scheme 1).[8d] However, in the reaction of N1-protected 4,6-unsubstituted 2-methylthiodihydropyrimidine **4** with amines, 4,6-unsubstituted 2-aminodihydropyrimidines **5** were not formed; instead, only unexpected products **6** were obtained by ring cleavage of the N1–C2 bonds (Scheme 1).[8e] These results led us to explore an alternative route to synthesizing related dihydropyrimidines.

We designed sequential reactions involving Staudinger reaction/aza-Wittig reaction/cyclization as a novel method of constructing the dihydropyrimidine skeleton.[9] Herein, we report the synthesis of 4,6-unsubstituted 2-aminodihydropyrimidine-5-carboxylates by using this strategy, as illustrated in Scheme 2. The Staudinger reaction of prepared (*E*)-ethyl 3-azido-2-{[(*tert*-butoxycarbonyl)amino]methyl}acrylate [(*E*)-**7**] with triphenylphosphine, followed by the aza-Wittig reaction of the resulting iminophosphorane (*E*)-**8** with isocyanates **9**, and intramolecular cyclization of the carbodiimide intermediates (*E*)-**10** furnished 4,6-unsubstituted 2-aminodihydropyrimidine-5-carboxylates **11**, which can be converted into N-unsubstituted products **12**.



Scheme 1 Attempted synthesis of less substituted dihydropyrimidines

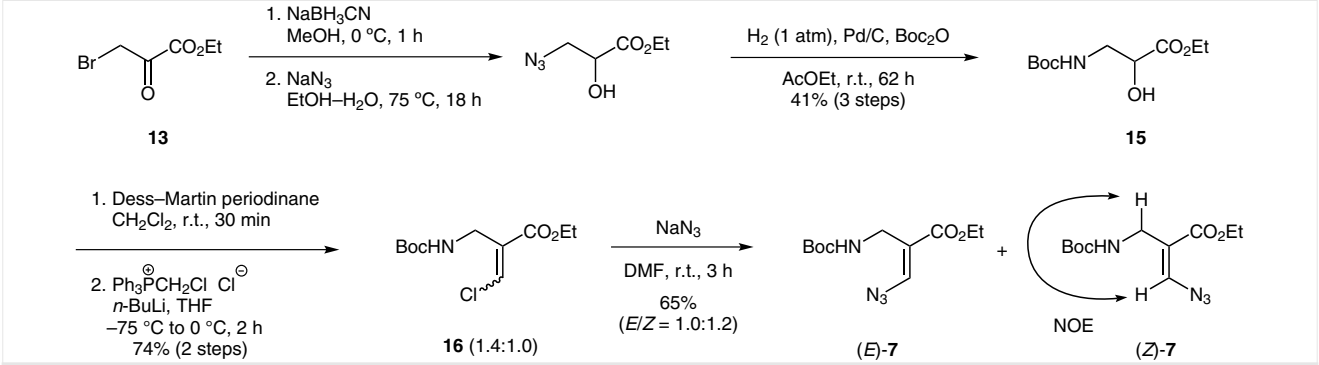


Scheme 2 Synthetic strategy for 4,6-unsubstituted 2-aminodihydropyrimidine-5-carboxylates **11** and **12**

In general, multisubstituted 2-aminodihydopyrimidines have been synthesized by three-component condensation using guanidines, aldehydes, and β-dicarbonyl compounds,[10] by cyclization of guanidines with α,β-unsaturated carbonyl compounds,[11] or by nucleophilic substitution reaction of 2-alkylthio[8d,12a] or 2-alkoxydihydropyrimidines[12b] with amines. For the synthesis of less substituted 2-aminodihydropyrimidines, several methods for providing 5,6-unsubstituted 2-amino-4-oxodihydropyrimidines[13] and only a few examples of reactions proceeding through the reduction of pyrimidines have been reported so far.[14] Our novel method is useful for synthesizing 4,6-unsubstituted 2-aminodihydropyrimidine-5-carboxylates, which are not easy to obtain by conventional methods. In fact, to our knowledge, the general formulae of **11** and **12** have not previously been reported.

First, ethyl 3-azido-2-{[(*tert*-butoxycarbonyl)amino]-methyl}acrylate (**7**) was prepared from ethyl bromopyruvate (**13**) in six steps, as shown in Scheme 3. As reported previously,[15] the reduction of **13** by using sodium cyanoborohydride and subsequent substitution reaction with sodium azide, afforded ethyl 3-azido-2-hydroxypropanoate (**14**). Subsequently, in a hydrogen atmosphere with 10% palladium on carbon and di-*tert*-butyl dicarbonate, the crude product **14** was converted into ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropanoate (**15**) in 41% isolated yield in three steps from **13**. The reaction conditions for oxidation of **15** were then examined; unfortunately, typical oxidation conditions using pyridinium dichromate (PDC), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), or oxallyl chloride and dimethylsulfoxide (Swern oxidation) were not effective, and the reactions either gave a complex mixture or resulted in the recovery of only **15**. However, we found that Dess–Martin periodinane was a suitable reagent and its application produced the desired α-keto ester in a high yield.[16] When the crude α-keto ester was subjected to the Wittig reaction using chloromethyltriphenylphosphonium chloride and *n*-butyllithium, ethyl {[(*tert*-butoxycarbonyl)amino]methyl}-3-chloroacrylate (**16**) was obtained as a mixture of stereoisomers (1.4:1.0) in 74% yield in two steps from **15**. The treatment of **16** with sodium azide afforded the two stereoisomers alkenylazide (*E*)-**7** and (*Z*)-**7** (1.0:1.2) in 65% yield, which were isolated by silica gel column chromatography. The structure of the major product (*Z*)-**7** was determined by NOE experiments. A significant NOE signal (1.3%) was observed between the methylene protons (δ 3.83 ppm) and the 3-proton (δ 6.98 ppm). Therefore, its structure was determined to be that shown as (*Z*)-**7**.

A sequential reaction was attempted in which the treatment of (*E*)-**7** with triphenylphosphine (1.2 equiv) in THF at room temperature for 15 min quantitatively yielded iminophosphorane (*E*)-**8**,[17] to which phenyl isocyanate **9a** (1.3 equiv) was added. The reaction mixture was stirred at the same temperature for 6 h, and the desired 4,6-unsubstituted 2-phenylaminodihydropyrimidine-5-carboxylate **11a** was obtained in 34% yield (Table 1, entry 1). In the ^{1}H NMR spectra of the crude reaction mixture, unreacted (*E*)-**8** was observed in 24% yield. When the amount of **9a** was increased to 2.5 equiv, (*E*)-**8** was completely consumed and the yield was improved to 56% (entry 2). When 5.0 equiv of **9a** was used, the reaction proceeded smoothly to give **11a**

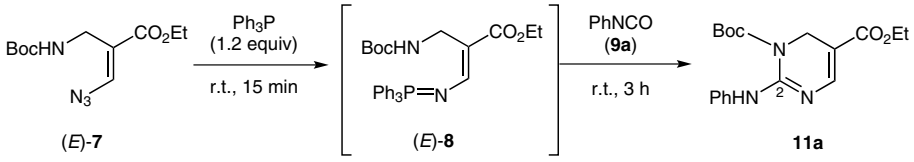


Scheme 3 Preparation of substrate **7**

in a high yield of 78% (entry 3). The use of an excess amount of **9a** (10 equiv) had no further positive effect and led to the production of an unidentified byproduct (entry 4). When a less polar solvent (i.e., dichloromethane or toluene) was used, the reactions resulted in lower yields of **11a** (entries 5 and 6). The use of DMF was also ineffective (entry 7). Hence, we used the reaction conditions detailed in Table 1, entry 3 to synthesize **11** from (*E*)-**7**.

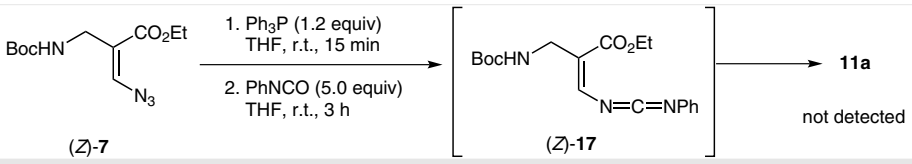
To determine the effect of the olefin geometry of **7** on the course of the reaction, (*Z*)-**7** was used as the starting material (Scheme 4). Under the optimized reaction conditions, **11a** was not obtained although nitrogen was generated during the reaction of (*Z*)-**7** with triphenylphosphine. This is probably because the carbodiimide intermediate (*Z*)-**17** does not undergo cyclization. Therefore, the olefin geometry of **7** is crucial, and only the use of (*E*)-**7** enables the successful construction of the dihydropyrimidine skeleton.

Table 1 Optimization of Reaction Conditions



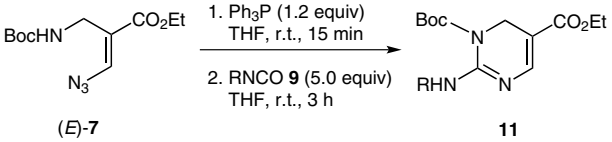
Entry	Solvent	**9a** (equiv)	Yield (%)
1[a]	THF	1.3	34
2	THF	2.5	56
3	THF	5.0	78
4	THF	10.0	67
5	CH_2Cl_2	5.0	65
6	toluene	5.0	64
7	DMF	5.0	36

[a] Reaction time with **9a** was 6 h, and (*E*)-**8** was recovered in 24% yield.



Scheme 4 Use of (*Z*)-**7** as the starting material

Table 2 Synthesis of 4,6-Unsubstituted 2-Aminodihydropyrimidines **11**



(*E*)-**7** **11**

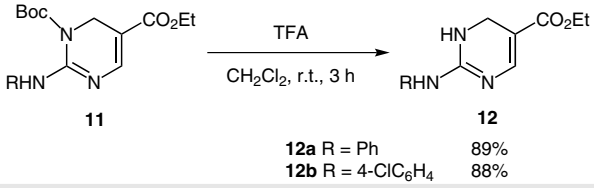
Entry	9	R	11	Yield (%)
1	**9a**	Ph	**11a**	78
2	**9b**	4-ClC_6H_4	**11b**	85
3	**9c**	4-$EtO_2CC_6H_4$	**11c**	92
4	**9d**	4-$F_3CC_6H_4$	**11d**	95
5	**9e**	4-$MeOC_6H_4$	**11e**	65
6[a]	**9f**	2-MeC_6H_4	**11f**	47
7	**9g**	1-naphthyl	**11g**	54

[a] Reaction time with **9f** was 12 h.

Under the optimized reaction conditions, aryl isocyanates **9** were subjected to sequential reactions with (*E*)-**7** to assemble 4,6-unsubstituted 2-arylaminodihydropyrimidine-5-carboxylates **11**.[18] The results are summarized in Table 2. Aryl isocyanates **9b**–**d**, with electron-withdrawing moieties such as 4-chloro, 4-ethoxycarbonyl, and 4-trifluoromethyl groups, showed high reactivities, giving **11b**, **11c**, and **11d** in excellent yields of 85, 92, and 95%, respectively (entries 2–4). Although isocyanate **9e**, with an electron-donating 4-methoxy group, exhibited a relatively low reactivity, the corresponding product **11e** was obtained in an acceptable yield of 65% (entry 5). Thus, the electrophilic properties of **9b**, **9c**, and **9d**, with an electron-withdrawing group at the 4-position, may accelerate their reaction with nucleophilic iminophosphoranes (*E*)-**8** and the cyclization of the carbodiimide intermediates (*E*)-**10**. Even sterically hindered 2-tolyl and 1-naphthyl isocyanates **9f**–**g** could be used in the reactions to obtain **11f**–**g** in moderate yields (entries 6 and 7).

When aliphatic benzyl isocyanate **9h** was reacted with (*E*)-**7**, in addition to dihydropyrimidine **11h** (16%), bicyclic dihydropyrimidine **18** was obtained as the major product in 52% yield (Scheme 5). Owing to the higher nucleophilicity of the benzyl amine moiety compared with that of the aryl amine moiety, **11h** reacted further with the remaining **9h**, and the subsequent second cyclization by an intramolecular substitution reaction with a *tert*-butoxycarbonyl group afforded **18**.

The N-protecting (Boc) group was easily removed to produce N-unsubstituted dihydropyrimidines **12** (Scheme 6). When **11a** was treated with trifluoroacetic acid (TFA) in dichloromethane at room temperature for 3 h, **12a** was obtained in 89% yield.[19] The deprotection of **11b** also proceeded to give **12b**. To analyze the tautomeric behavior of **12a** and **12b**, ^{1}H NMR spectra of **12** were measured in CD_3OD, $CDCl_3$, and DMSO-d_6 at 25 °C (0.01 M, 600 MHz). In all these solvents, **12a** and **12b** were observed as single isomers, the behaviors of which were the same as those of 2-aminodihydropyrimidines.[8d,20] However, in our previous report on the synthesis of 4,6-unsubstituted 2-phenyl derivatives,[8b] their individual tautomers were observed in DMSO-d_6. As reported previously by Cho and co-workers,[20] it was found that the nature of the 2-substituents (phenylamino or phenyl group) on 4,6-unsubstituted dihydropyrimidines affects the tautomeric behavior.

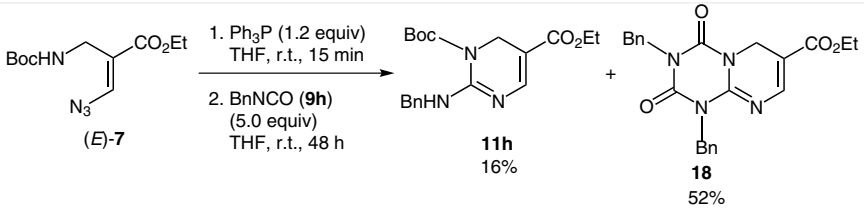


11 **12**

12a R = Ph 89%
12b R = 4-ClC_6H_4 88%

Scheme 6 Deprotection of **11**

In summary, a novel method of constructing the dihydropyrimidine skeleton was developed, which involves Staudinger reaction, aza-Wittig reaction, and cyclization. In addition to the methods presented in our previous reports, namely, [4+2] cyclization[8a–c] and nucleophilic substitution reaction,[8d] the one-pot sequential reactions for the synthesis of less substituted dihydropyrimidines were disclosed. We applied the method to the synthesis of 4,6-unsubstituted 2-aminodihydropyrimidine-5-carboxylates in this study. Given that dihydropyrimidines **11** and **12** were previously unavailable and difficult to synthesize by conventional methods, this unprecedented achievement should contribute to an expansion of dihydropyrimidine-based chemistry and pharmaceutical sciences for drug development.



(*E*)-**7** **11h** 16% **18** 52%

Scheme 5 Reaction of (*E*)-**7** with benzyl isocyanate **9h**

Acknowledgment

This work was financially supported by the Sasakawa Scientific Research Grant from The Japan Science Society and JSPS KAKENHI Grant Number 24790122 and 26810095.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378932.

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(17) Although (*E*)-**8** was not isolated because of its instability under silica gel column chromatography, its structure was determined by ^{1}H NMR analysis. The reaction of (*E*)-**7** with triphenylphosphine (1.2 equiv) in $CDCl_3$ at r.t. for 15 min quantitatively gave (*E*)-**8**.
(18) Under an argon atmosphere, to a solution of (*E*)-**7** (27.0 mg, 0.100 mmol) in THF (1.5 mL) was added triphenylphosphine (31.5 mg, 0.120 mmol). The reaction mixture was stirred at r.t. for 15 min, then phenyl isocyanate **9a** (54 µL, 0.499 mmol) was added, and stirring was continued at the same temperature for 3 h. To the reaction mixture was added EtOAc (20 mL), followed by sat. aq $NaHCO_3$ (5 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 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 silica gel column chromatography (*n*-hexane–EtOAc–Et_3N, 40:2:1) to give **11a** (26.8 mg, 0.0776 mmol, 78%) as pale-yellow crystals [mp 113–114 °C (*n*-hexane)].
(19) To a solution of **11a** (57.0 mg, 0.165 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.490 mL, 6.60 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 3 h, and aqueous 2 M NaOH (5 mL) and EtOAc (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). 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 recrystallization (*n*-hexane–EtOAc) to give **12a** (35.9 mg, 0.146 mmol, 89%) as colorless crystals (mp 192 °C).
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