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DIHYDROPYRIMIDINE

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Abstract – The synthesis history, physical properties (stability and tautomerism), ring construction procedures, a variety of reactions, various skeletons (monocyclic, bicyclic, tricyclic, tetracyclic, bicyclo-, and spiro-), and biological activities of dihydropyrimidines are reviewed.

CONTENTS

I. INTRODUCTION

Biginelli reported the first synthesis of dihydropyrimidines (3,4-dihydropyrimidin-2(1*H*)-ones) **1a** in 1891.[1] Since then, many researchers, Kappe,[2] Cho,[3a] Atwal,[4] and so on, have studied the reactivity, physical properties, synthetic mechanism and various analogue syntheses of **1** and **2**.[3b] A review on dihydropyrimidines **1** was described in 1993 under the title: 100 years of the Biginelli dihydropyrimidine synthesis by Kappe.[2a] On the other hand, the synthesis of the other types of dihydropyrimidine **3** was first reported in 1899 by Traube and Schwarz,[5] followed by only a few researchers, Ruhemann,[6] Dodson,[7] Heyes,[8] and Silversmith.[9] Dihydropyrimidines **1** and **2** could be regarded as keto-forms of the general chemical structure of **3**. The reported chemical structures of **3** were initially poorly characterized because of the lack of NMR spectra in those days. Thus, in some cases, the chemical structure is ambiguous and complicated owing to tautomerism and the isomerization of double bonds. Namely, dihydropyrimidines theoretically have nine isomeric mixtures including tautomers, which are oxidized to the corresponding

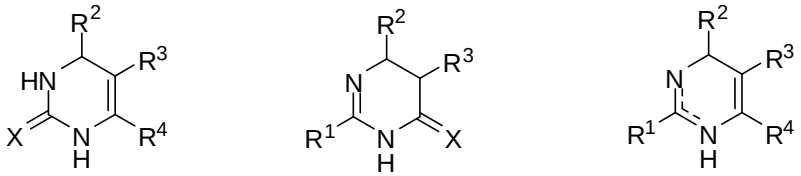


Figure 1. Two types of monocyclic dihydropyrimidines **1** and **3**

pyrimidines by atmospheric oxygen.[10] Therefore, reports on the synthesis and chemistry of **3** were very limited until those by recent independent research groups of Weis,[11] Kashima,[12] and Cho[3] came out. Since then, the chemistry of such compounds has been clarified and a variety of synthetic procedures for pharmacological active compounds[2h,4d,e,3i,13-16] and anti-oxidants for materials science[17] have been carried out (See section VI, Biological activities).

Although the review by Weis[11d] on the Traube and Schwarz dihydropyrimidines **3** appeared in 1986, the synthesis and reaction of **3** have already made progress over the past three decades. Therefore, a new description of dihydropyrimidines **3** may be useful for many future researchers in heterocyclic chemistry and medicinal chemistry. In view of these circumstances, the present review was prepared.

II. PHYSICAL PROPERTIES OF MONOCYCLIC DIHYDROPYRIMIDINES

(1) Structure and Stability

When it has different substituted groups, dihydropyrimidine (DP) could be theoretically represented as nine isomers including tautomers. For convenience in comparing DP isomers, informal names are given in parentheses in Figure 2, except for the IUPAC formal nomenclature. There are two types of dihydropyrimidine in terms of chemical structure, namely, enamines (1,4-DP, 1,6-DP, and 1,2-DP) and imines (2,5-DP and 4,5-DP). A cyclic enamine is usually more stable than its corresponding imine in contrast to acyclic compounds. Therefore, it is supposed that 2,5-DP and 4,5-DP are more unstable than 1,4-DP, 1,6-DP, and 1,2-DP. Thus, imines might isomerize to more stable 1,4-DP and 1,6-DP during preparation, storage or under acidic conditions. In fact, an example conversion from an imine to an enamine will be shown later (Scheme 17, eq. 46). As for the substituent effect, an electron-withdrawing group (R^3) at the 5-position and an electron-donating group (R^1) could stabilize the DP skeleton (1,4-DP and 1,6-DP),[11e] and electron-donating groups (R^2 and R^4) at the 4- and 6-positions could also stabilize the skeleton (1,2-DP and 2,5-DP).[11b] However, Kashima observed a new tautomeric equilibrium between 4,5-DP and 1,6-DP in 2-dimethylamino-4,6,6-trimethyldihydropyrimidine, and suggested the existence of an imine 4,5-DP isomer as determined by an IR spectrum.[12a] On the other hand, an imine-enamine tautomerism by which the enamine 1,2-DP isomerizes to the imine 2,5-DP as reported.[11c,d,g] Weis synthesized various DPs, as will be described later, and studied the stability of DPs. In particular, the isolation of less substituted dihydropyrimidines, for instance, monosubstituted DPs (R^1=C_6H_5, Me; R^2=R^3=R^4=H in Figure 2) was undertaken. Among them, 2-phenyldihydropyrimidine was stable, but 2-methyldihydropyrimidine was decomposed. The dihydropyrimidine (R^1=R^2=R^3=R^4=H) without any substituted group was extremely unstable and could not be isolated in pure state.[11h]

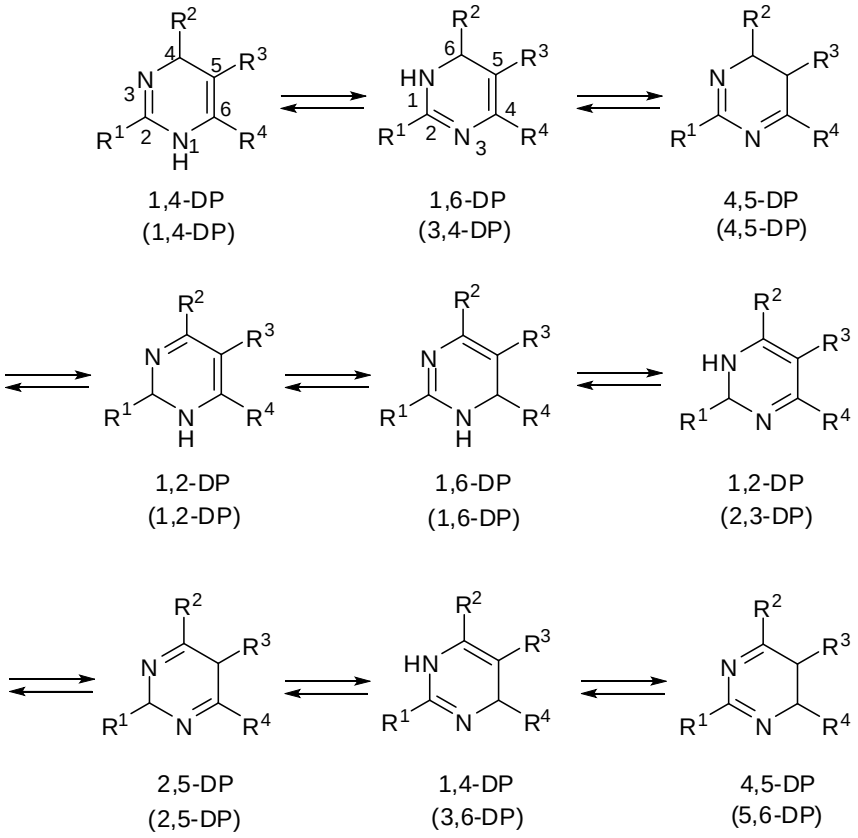


Figure 2. IUPAC nomenclature of dihydropyrimidines (convenient informal names are given in parentheses)

(2) Tautomerism

The [1,3]-sigmatropic tautomerism in the case of amidinic systems may be expressed in Figure 3 (eq. 1). Three classes of tautomeric equilibria can be distinguished according to the molecular structure of amidinic compounds: (1) acyclic (eq. 2), (2) semicyclic (eq. 3), and (3) cyclic or annular compounds (eq. 4). As for the tautomerism of cyclic amidines, studies of a five-membered ring, for instance, imidazoles, were extensively performed.[18] As for a six-membered ring, the tautomerism of dihydropyrimidines had not been studied until the report by Weis and Mamaev in 1975.[11a] A dihydropyrimidine is usually observed as a single compound in an NMR spectrum, but it is actually a mixture of 1,4-DP and 1,6-DP. Proton transfer from one nitrogen atom to the other is very fast and the NMR spectrum usually resembles that of a single compound just like that of an imidazole derivative. Regarding the dihydroform of DPs in solution, Weis suggested that, under certain experimental conditions, solutions of substituted dihydropyrimidines exhibited two independent NMR peaks for the two tautomeric species.[11a] Subsequently, van der Plas[19a,b] and Girke[20] independently studied the behavior of a variety of dihydropyrimidines. They attempted to obtain the NMR spectra in deuteriochloroform ($CDCl_3$) of each of the tautomers (type **a** and type **b**), but failed even at -88 °C.

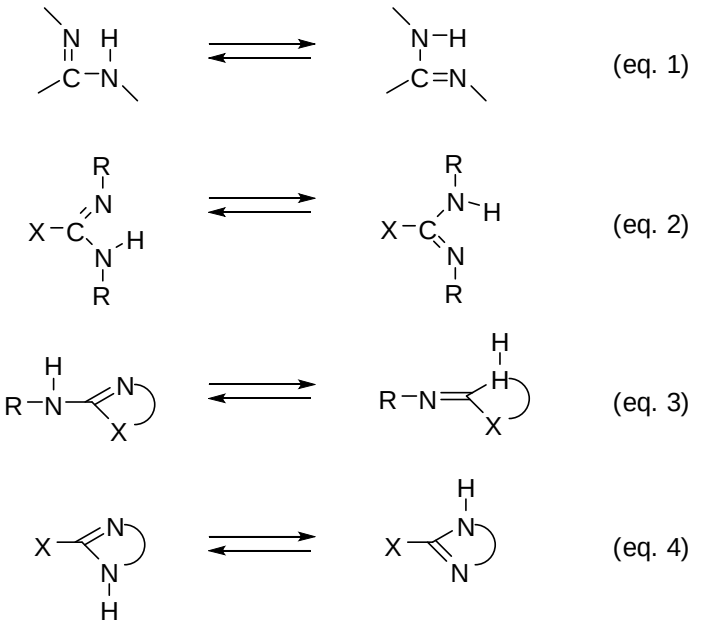


Figure 3. Tautomeric equilibria

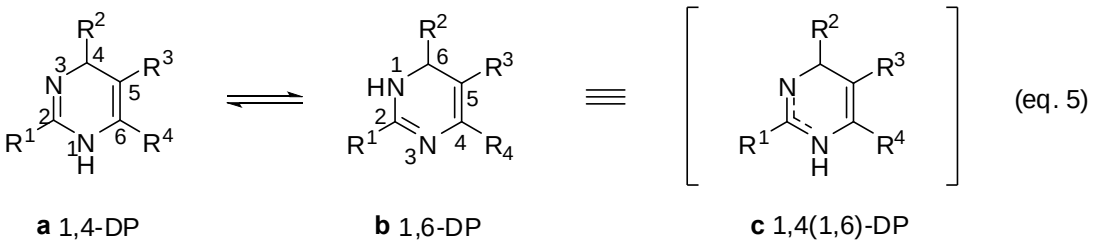


Figure 4. Tautomerism of 1,4-DP (**a**) and 1,6-DP (**b**)

Weis again studied the tautomerism of 6(4)-methyl-2,4(6)-diphenyl-1,4(1,6)-dihydropyrimidines **4** (R^1=R^2=C_6H_5; R^3=H; R^4=Me) and observed two individual tautomers **4a** and **4b** (Figure 4) at -50 °C in a dilute $CDC1_3$ solution (0.001-0.003 M).[11b] Because $CDCl_3$ contains a small amount of HCl, which causes the rapid proton transfer between two nitrogen atoms, it should be purified through dry Al_2O_3 or distilled over P_2O_5 and then through dry Al_2O_3.[11c] Dihydropyrimidine exhibits a characteristic nature in crystalline state. Initially, Weis reported that a tautomeric mixture of **4** existed in only 1,4-DP form in a crystal by X-ray crystallographic analysis, but isomerized to an equilibrium mixture of 1,4- and 1,6-DPs in solution.[11b] This phenomenon depends on DP derivatives[3g,j] and is not always observed in all dihydropyrimidines. Subsequently, Cho and Taira carried out an X-ray crystallographic analysis of 4-(2-chlorophenyl)-5-ethoxycarbonyl-2,6-dimethyl-1,4(1,6)-dihydropyrimidine **5** and found it to exist in only the electron-localized 1,4-dihydro form **5a** with a flat-boat conformation in crystalline state; however, in solution, **5a** isomerized to a mixture of dihydropyrimidines, **5a** (1,4-DP; major) and **5b**

(1,6-DP; minor).[3e] Also, they obtained a very rare result of the X-ray crystallographic analysis of 6-chloro-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-methyldihydropyrimidine 1/2 HCl salt **6** prepared after extractive work-up under basic condition (Figure 5). The data showed that the unit cell contained two different molecules with Cl atoms: the molecules of the electron-localized 1,4-dihydro form and electron-delocalized form. Both forms were linked by hydrogen bonding around the center of symmetry in the unit cell.[3e]

As for other examples showing different chemical structures in solid state and solution, the keto-enol tautomerism of curcumin, a natural product, was reported.[21] Curcumin is in keto form in solid state, but in an enol form as a major component in solution.

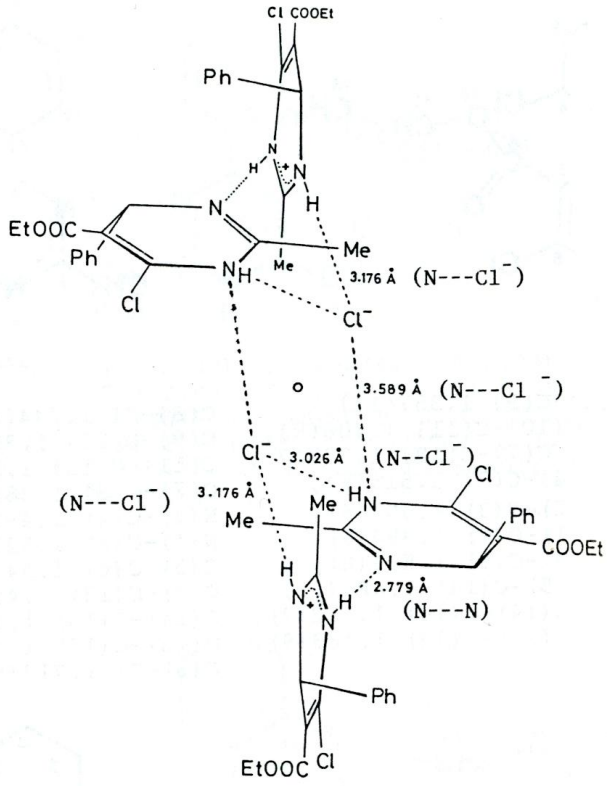


Figure 5. The X-ray crystallographic analysis of 6-chloro-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-methyldihydropyrimidine 1/2 HCl salt **6**

Cho and Iwashita synthesized **7** (R^1=CF_3; R^2=*o*-$NO_2C_6H_4$; R^3=CO_2Pr-*i*; R^4=Me, Figure 4) and observed the individual tautomers **7a** and **7b** at room temperature in condensed solution (C_6D_6, 0.123 M),[3g] although it is generally presumed that tautomers could sometimes be observed at very low temperatures below 0 °C and in highly dilute solutions.[19c] Moreover, they demonstrated that the nature of the substituted groups (CF_3, SMe, C_6H_5, NMe_2, H, Me, *i*-Pr) at the 2-position affected the observation, whether the signals of individual isomers or the average signals of both isomers were found on an NMR

spectrum. An electron-withdrawing group (CF_3) at the 2-position afforded independent tautomers (with 1,4-DP as the major tautomer and 1,6-DP as the minor tautomer), because the proton transfer may be slow owing to the low electron density on nitrogen. On the other hand, an electron-donating group (NMe_2) afforded only one tautomer, 1,6-DP. This may be due to the stabilizing effect by both the NMe_2 group and the electron-withdrawing group, CO_2Pr-*i*.[3g] Subsequently, Nishimura and Yasui synthesized **8** (R^1=SMe; R^2=H; R^3=CO_2Et; R^4=Me, Figure 4) and found the individual tautomers **8a** and **8b**[3j] (Figure 6) and observed that the ratio of 1,4-/1,6-DP in DMSO-d_6 gradually changed by the concentration and temperature (Table 1).

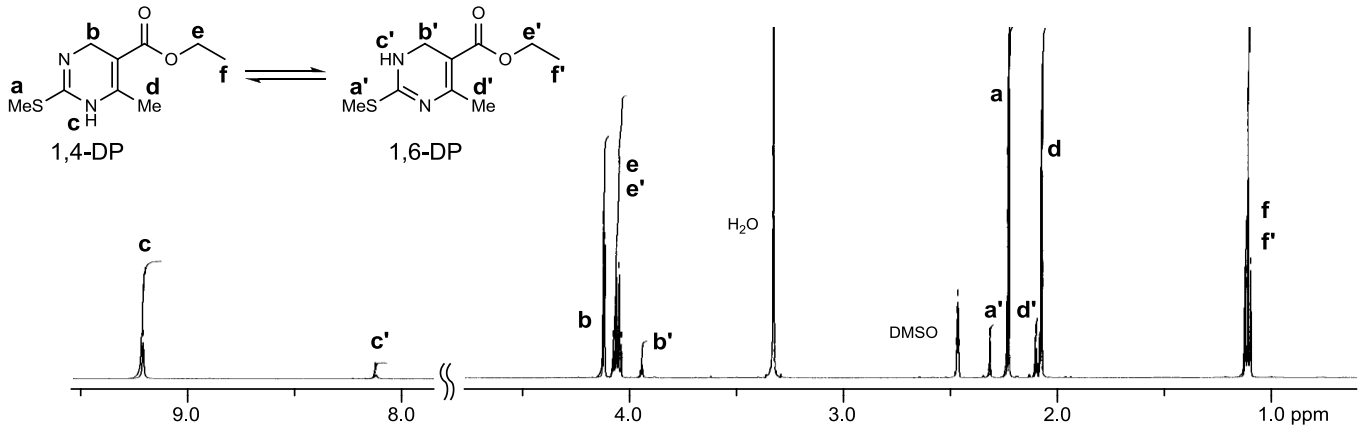


Figure 6. ^{1}H NMR of the tautomeric mixture, **8a** (1,4-DP: major) and **8b** (1,6-DP: minor), (0.100 M, 25 ^{o}C) in DMSO-d_6.

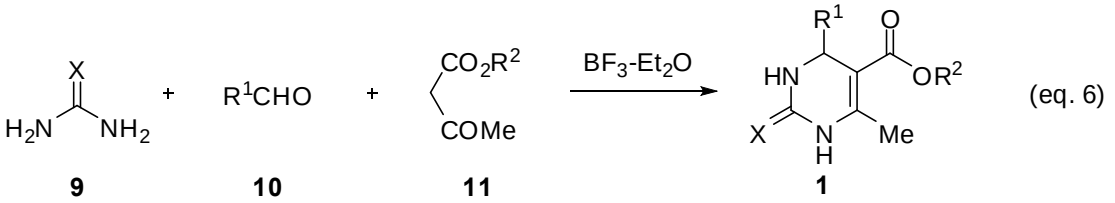
Table 1. Tautomerization of ethyl 6-methyl-2-methylsulfanyl-1,4-dihydropyrimidine-5-carboxylate **8a** and ethyl 4-methyl-2-methylsulfanyl-1,6-dihydropyrimidine-5-carboxylate **8b** in ^{1}H-NMR in DMSO-d_6

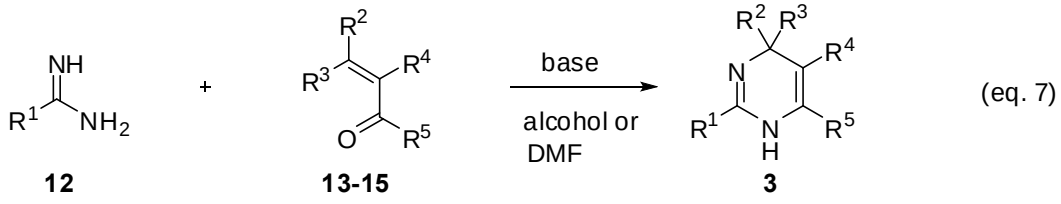
Concentration (M)	Temperature (^{o}C)	Ratio of 1,4-/3,4-DP
0.012	25	7.0
0.025	25	6.8
0.050	25	6.6
0.100	25	6.5
0.050	15	7.5
0.050	35	6.1
0.050	45	5.9
0.050	55	5.4
0.050	65	4.7
0.050	75	4.4
0.050	85	4.2
0.050	95	average spectrum

III. SYNTHETIC METHODS OF MONOCYCLIC DIHYDROPYRIMIDINES

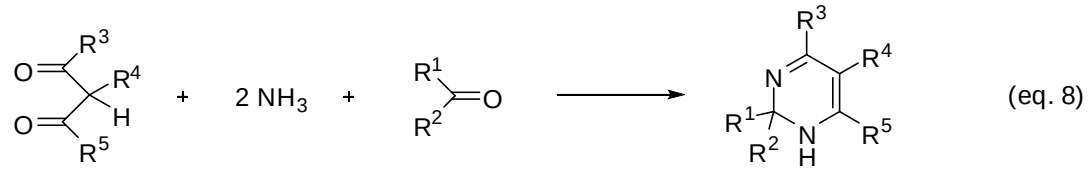
1) Cyclization

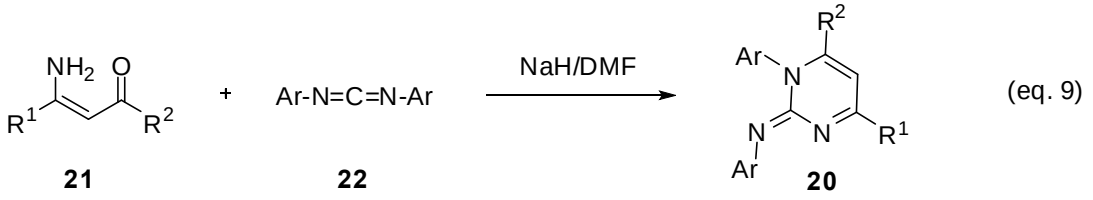
The construction procedures of dihydropyrimidine skeletons should be classified into five types, as shown in Scheme 1.

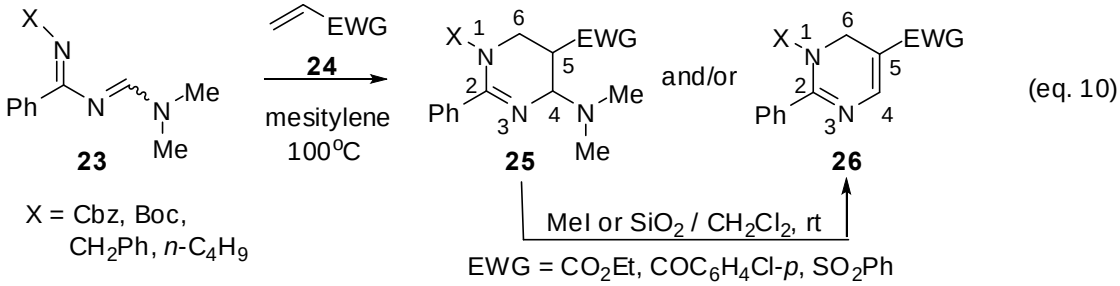




R^1 = alkyl, aryl, H, CF_3, NHR', OR', SR'
R^2 = alkyl, aryl; R^3 = H, alkyl; R^4 = H, alkyl, CO_2R
R^5 = O-alkyl, alkyl







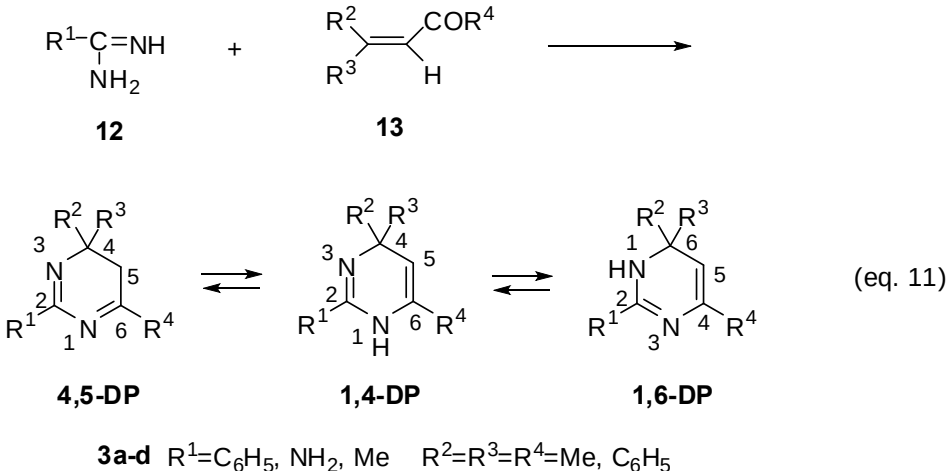
Scheme 1. Construction of dihydropyrimidine skeletons by cyclization

(1) Cyclization using urea (Biginelli reaction) (Scheme 1, eq. 6)

Biginelli reported the first syntheses of dihydropyrimidines **1a**: 3,4-dihydropyrimidin-2(1*H*)-ones (R^1=C_6H_5; R^2=Et; X=O) (eq. 6) by a one-pot condensation reaction of urea **9a** (X=O), an aromatic aldehyde **10**, and ethyl acetoacetate **11a** in EtOH.[1] Many studies have been performed since then and the review[2a] mentioned above explains the synthesis, reactions and reaction mechanism of dihydropyrimidin-2(1*H*)-ones.[2d,3a] Similarly, 3,4-dihydropyrimidin-2(1*H*)-thiones **1b** (R^1=H, aryl, alkyl; X=S) were obtained using thiourea **9b** instead of urea **9a**.[3j,4c,22] Alternatively, the thioxo derivatives **1b** were obtained by the thiocarbonylation of **1a** with P_2S_5 or Lawesson reagent.

(2) Cyclization using benzamidine, acetamidine and guanidine (Scheme 1, eq. 7 and Scheme 2)

In 1899, Traube and Schwarz firstly synthesized dihydropyrimidines **3**. The cyclization of benzamidine **12a** (R^1=C_6H_5) with mesityl oxide **13a** (R^2=R^3=R^4=Me; R^5=H) afforded 4,4,6-trimethy-2-phenyldihydropyrimidine **3a**, but the chemical structure of **3a** was described to be an imine: 4,5-DP (Scheme 2).[5] They also performed the cyclization of guanidine **12b** (R^1=NH_2) with **13a** and obtained dihydropyrimidine, suggested to be 2-amino-4,4,6-trimethyl-4,5-dihydropyrimidine **3b**. Successively, Ruhemann found that the reaction of **12a** with 3-benzylidene-2,4-pentanedione **13b** (R^2=C_6H_5; R^3=H; R^4=COMe; R^5=Me) (eq. 7) at 100 °C resulted in the loss of an acetyl group with the formation of methyldiphenyldihydropyrimidine **3c**, whose proposed chemical structure was 1,4-DP.[6] Dodson and Seyler used the reaction of **12a** with various α-benzylidene ketones **13** for the preparation of 6-methyl-2,4-diphenyldihydropyrimidines **3d**.[7] Thus, the chemical structures were ambiguous in those days because of the lack of NMR instruments.

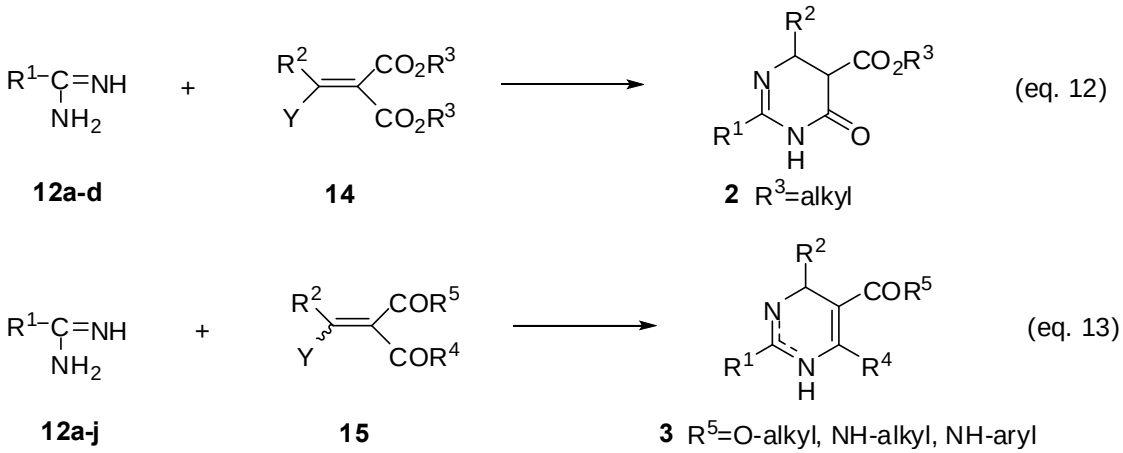


(eq. 11)

Scheme 2. The synthesis of dihydropyrimidines from benzamidine and α, β-unsaturated ketones

Weis synthesized various dihydropyrimidines **3** in good yields by this procedure[11h] and studied their stability and tautomerism. On the other hand, Kashima and Omote synthesized 1,6-dihydro-4,6,6-

trimethypyrimidine **3e-k**, substituted at the 2-position with phenyl, Me, *i*-Pr, OEt, SMe, NMe_2, and H to investigate the substituent effects on the properties of dihydropyrimidines.[12a,b] They also transformed SMe-dihydropyrimidine **3i** with NaOR in ROH to OMe-dihydropyrimidine **3l**.[12g] Cho and coworkers synthesized various 5-alkoxycarbonyl-4,5-dihydropyrimidin-6(1*H*)-ones **2** and 5-alkoxycarbonyl-1,4(1,6)-dihydropyrimidines **3** to find pharmacologically active derivatives (eq. 13). The cyclization of 3-substituted 2-alkoxycarbonyl-2-propenoate **14** (Y=H) with **12a-d** (R^1=C_6H_5, NH_2, NMe_2, Me) in the presence of NaOR afforded compounds **2** (R^1=C_6H_5, NH_2, NMe_2, Me; R^2=substituted phenyl, furyl, thienyl, pyridyl, alkyl; R^3=Me, Et, *i*-Pr) (eq. 12), which were generally stable.[3b] The stereochemistry of the 4 and 5-positions depended on the manner of substitution of a functional group on a phenyl group [*trans*/*cis*=3/2-2/1(*ortho*); 9/1(*meta*); only *trans* (*para*)].[3b] Similarly, the condensation of alkyl 2-acetyl-3-aryl-2-propenoate **15** (Y=H) with **12** (benzamidine, guanidine, 1,1-dimethylguanidine, or acetamidine) followed by the dehydration of the resulting tetrahydropyrimidine with *p*-TsOH or Al_2O_3 yielded a series of 1,4(1,6)-dihydropyrimidines **3** (R^1=C_6H_5, NH_2, NMe_2, Me, *i*-Pr, CF_3, H, SMe; R^2=C_6H_5, *o*- or *m*-$NO_2C_6H_4$, *o*- or *m*-ClC_6H_4, *o*-BrC_6H_4, *p*-$SMeC_6H_4$; R^4=Me; R^5=OMe, OEt, OPr-*i*, O-cyclopropylmethyl) in good to excellent yields, except dihydropyrimidines with R^1=NH_2 and NMe_2 (eq. 13).[3c,g,i] Other dihydropyrimidines with a variety of long chains (R^4=$CH_2OCH_2CH_2NR^6R^7$) at the 6-position produced by cyclization were also prepared.[3c] As other examples of cyclization, Atwal and coworkers also synthesized a series of 1,4(1,6)-dihydropyrimidines **3** (R^1=SMe, OMe; R^5=O-alkyl)[4d,24,25] by the condensation of commercially available 2-methyl-2-thiopseudourea sulfate **12h** (R^1=SMe)[4d] or *O*-methylisourea hydrogensulfate **12i** (R^1=OMe)[4a] and α-benzylidene-β-keto ester **15** in the presence of NaOAc or $NaHCO_3$, although alkylthiopseudoureas **12j** (R^1=$SCH_2C_6H_4OMe$-*p*) required for this method were obtained by the alkylation of thiourea **9b**.[4a,d] According to Cho's and Atwal's reports, many researchers have tried to synthesize a variety of compounds **3.** Especially, in the case of an amino group



Scheme 3. General synthetic method for 5-alkoxycarbonyl-4,5-dihydropyrimidin-6(1*H*)-ones **2** and 5-alkoxycarbonyl-1,4 (1,6)-dihydropyrimidines **3**

at the 2-position, an improvement in the yield of **3** (R^1=NH_2; R^2=aryl; R^4=alkyl; R^5=O-alkyl) was carried out with the aid of a microwave by Kappe.[2g] Subsequently, various compounds **3** (R^1=R^2=R^4=alkyl; R^5=O-alkyl; or R^1=SMe; R^2=R^4=alkyl; R^5=O-alkyl)[26,27] with alkyl substituents at both the 2 and 4-positions were synthesized. As for dihydropyrimidines with an amide group at the 5-position, amides **3** (R^1=substituted NH, aryl; R^2=aryl; R^4=Me; R^5=NH-alkyl,[28] NH-aryl[29]) were provided by direct cyclization (eq. 13).[28,29]

When the β-substituent (Y) of **14** and **15** is any leaving group instead of a proton (Y=H), the condensation reaction does not give dihydropyrimidines, but it affords their corresponding pyrimidines.

(3) Cyclization using ammonia (Hantzsch type reaction) (Scheme 1, eq. 8)

The four-component condensation reaction of the 1,3-dicarbonyl compound **16** with two moles of ammonia (or ammonium salts) **17** and another carbonyl compound **18** seems to be a convenient approach to preparing 1,2-dihydropyrimidines **19**. This reaction is nearly identical to the Hantzsch synthesis of dihydropyridines. The first successful isolation of 1,2-dihydropyrimidines **19** was achieved by Hoffmann and coworkers,[23] but their procedure seems to be limited and to depend on the substituted functional groups.

(4) Cyclization of α,β-unsaturated-β-aminoketone with diarylcarbodiimides (Scheme 1, eq. 9)

A new method of constructing a dihydropyrimidine ring was reported by Katoh and Kashima.[12d] 4,6-Disubstituted-1-aryl-2-arylimino-1,2-dihydropyrimidines **20** (R^1, R^2=Me, *n*-C_3H_7, C_6H_5, *p*-ClC_6H_4) were conveniently synthesized in high yields by the reaction of α,β-unsaturated-β-aminoketones **21** with diarylcarbodiimides **22** in the presence of a large excess of NaH in DMF at -25 °C. Since this synthetic method is limited to the examples given and was not subsequently studied by other researchers, the position of the C-N bond formation of a dihydropyrimidine ring remains unknown (Figure 7).

(5) Cyclization of 1,3-diaza-1,3-butadienes with α,β-unsaturated carbonyl compounds (Scheme 1, eq. 10)

1,3-Diaza-1,3-butadienes are useful for the synthesis of pyrimidinone,[30,31,32] heterocyclic fused pyrimidinone,[31b-d] or pyrimidine,[32,33] but have never been used for the synthesis of dihydropyrimidines. The nearly unsolved problem in the field of dihydropyrimidine synthesis concerns the method of synthesizing less substituted dihydropyrimidines.[11h-j] Cho and coworkers investigated a novel method of constructing a dihydropyrimidine skeleton by the reaction of 1,2,4-trisubstituted-1,3-diaza-4-dimethylamino-1,3-butadienes **23** having an *N*-protecting group (*N*-Cbz, *N*-Boc, *N*-alkyl, or *N*-benzyl) with α,β-unsaturated carbonyl compounds **24** such as ethyl acrylate and *p*-chlorophenyl vinyl ketone.[3m,n] Consequently, 4-dimethylamino-2-phenyl-1,4,5,6-tetrahydropyrimidines **25** were obtained in good yields. Subsequently, the β-elimination of the dimethylamino group was carried out with MeI in CH_2Cl_2 or

SiO_2/molecular sieves 3Å in CH_2Cl_2 to afford various *N*-protecting-2,5-disubstituted-1,6-dihydropyrimidines **26** in good yields (Scheme 1, eq. 10). Remarkably, the use of phenyl vinyl ketone or 4-chlorophenyl vinyl ketone directly provided **26** in over 90% yield without the formation of tetrahydropyrimidine intermediates **25**.[3m,n] These results were considered to be due to the effective β-elimination of the dimethylamino group of **25** supported by the notion that the high acidity of α-hydrogen at the 5-position was enhanced by the carbonyl group (eq. 10). After the removal of the protecting group, less substituted dihydropyrimidines **26** (X=H) were furnished. The protecting group (R) is attached at the 1-position of 1,3-diaza-1,3-butadiene to stabilize itself as well as to control the reactivity during cyclization.

In summary, the construction procedures for a dihydropyrimidine skeleton should be classified into five types and the positions of the bond formation are drawn in Figure 7. Methods (1) and (2) should be reliable for various derivatives and method (5) may be promising for extensive synthetic research.

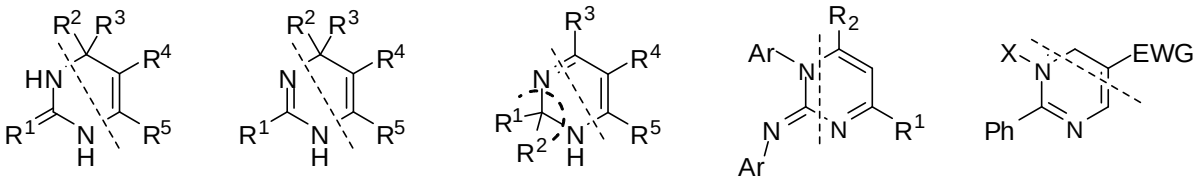
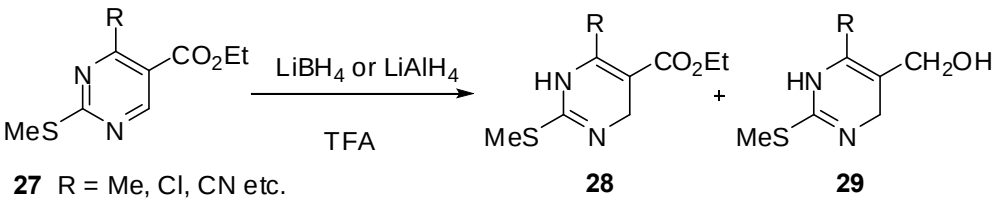


Figure 7. The positions for the bond formation of five dihydropyrimidines

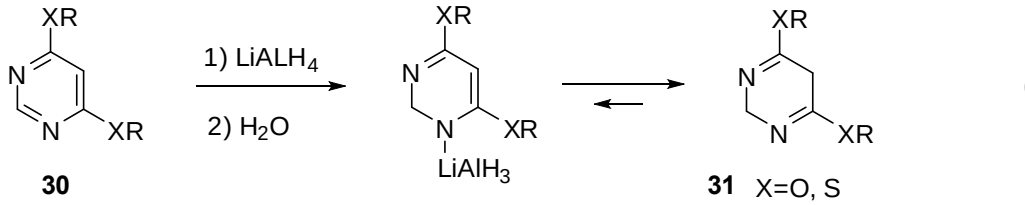
2) Reduction

The second synthetic procedure of dihydropyrimidines is reduction using hydrides as reagents; Et_3SiH, $LiBH_4$, and $LiAlH_4$. Only a few synthetic examples of dihydropyrimidines (or/and tetrahydropyrimidines) given by the direct reduction of a pyrimidine skeleton were reported. Shadbolt tried the direct reduction of pyrimidines **27** with $LiBH_4$ or $LiAlH_4$, and obtained a mixture of 1,4-dihydropyrimidines **28** and **29** (Scheme 4, eq. 14).[34] Weis studied the reduction of pyrimidines **30** having two electron-donating groups (OMe, SMe, OEt, OPr-*n*, or OBu-*n*) at the 4- and 6-positions neighboring two nitrogen atoms, and after equilibrium obtained 2,5-dihydropyrimidines **31** (imine-dihydropyrimidines) in 79-95% yields (eq. 15).[11e] Recently, Shen has also demonstrated the reduction of aminopyrimidine **32** with triethylsilane (Et_3SiH) and trifluroacetic acid (TFA) to obtain a 1:1 mixture of 1,6-dihydropyrimidine **33** and 1,4,5,6-tetrahydropyrimidine **34** (eq. 16).[35] Kashima and Omote prepared ethyl 1-benzyl-1,4-dihydro-2,6-dimethylpyrimidine-5-carboxylate **35** by the desulfurization of **36**[12c,e,f] under hydrogen for 3 h in the presence of Raney nickel in MeOH at room temperature and compared its nature with that of the corresponding dihydropyridine (Scheme 4, eq. 17).

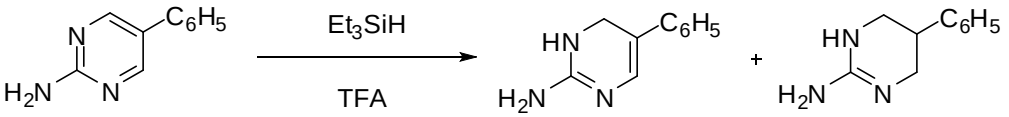
However, the synthetic procedures for dihydropyrimidines with various substituted groups often give a mixture of dihydropyrimidine and tetrahydropyrimidine. Therefore, to obtain a dihydropyrimidine skeleton, the general cyclization procedures mentioned previously are recommended.



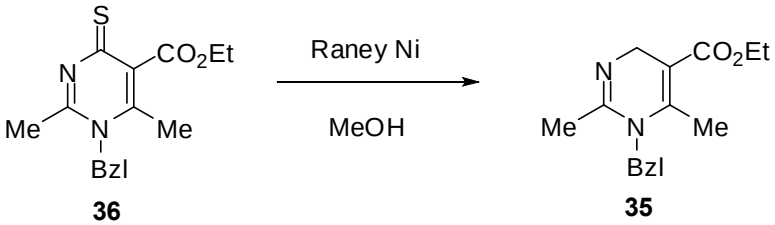
27 R = Me, Cl, CN etc. **28** **29** (eq. 14)



30 **31** X=O, S R=Me, Et, *n*-Pr, *n*-Bu (eq. 15)



32 **33** **34** (eq. 16)



36 **35** (eq. 17)

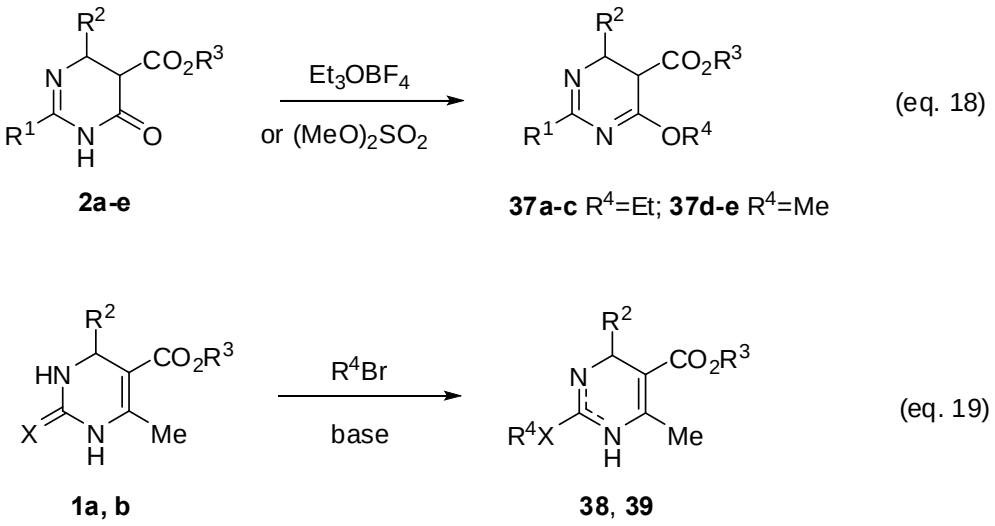
Scheme 4. Construction of dihydropyrimidine skeleton by reduction

IV. REACTIONS

Conversion from a dihydropyrimidine into another dihydropyrimidine derivative has been extensively studied by a lot of groups, and various reactions have been discovered and developed.

(1) *O*-Alkylation

The treatment of dihydropyrimidinone **2a-c** (R^1=Me; R^2=C_6H_5, 2-furyl, 2-thienyl; R^3=Et) with Meerwein reagent (Et_3OBF_4/CH_2Cl_2) or **2d-e** (R^1=Me; R^2=*m*-BrC_6H_4, 2-pyridyl; R^3=Me) with dimethyl sulfate and K_2CO_3 in MeOH afforded imine-dihydropyrimidines **37a-c** (R^4=Et: 42%, 21%, 23%) or **37d-e** (R^4=Me: 44%, 39%), respectively (eq. 18).[3d] On the other hand, the *O*-alkylation of Biginelli dihydropyrimidine **1a**



Scheme 5. *O*- and *S*-Alkylation of dihydropyrimidines **1** and **2**

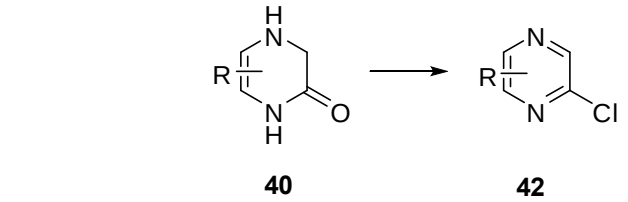
(X=O) in the presence of $NaHCO_3$ in *N*,*N*-dimethylformamide at 70 °C furnished the *O*-alkylated compound **38** (XR^4=O-allyl, OMe; R^2=C_6H_5; R^3=Et)(eq. 19).[26]

(2) *S*-Alkylation

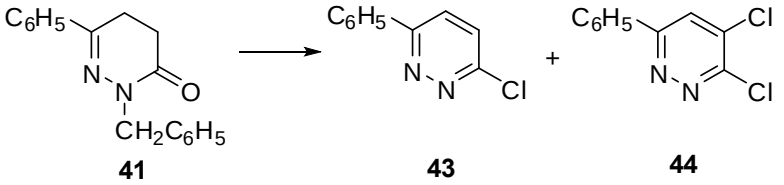
S-Alkylation at the 2-position of the dihydropyrimidine **1b** (X=S) with alkyl halide was performed in the presence of a base (K_2CO_3 or pyridine) by a lot of research groups to provide the corresponding *S*-alkylated 1,4(1,6)-dihydropyrimidines **39** (XR^4=SMe, SC_5H_{11}, $SCH_2COC_6H_5$, SCH_2CO_2H *etc.*; R^3=Et) in excellent yields (eq. 19).[3g,4d,36-40] As mentioned in the section of cyclization (eq. 13), some of the compounds could be obtained by the direct condensation of *S*-alkylthiourea with α,β-unsaturated ketoesters.[4d]

(3) Halogenation

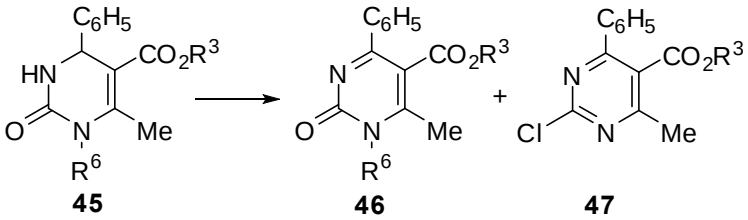
Although the chlorination of carbonyl groups of organic compounds and heterocycles is easily achieved, it is very difficult to obtain chlorinated dihydroheterocycles. Namely, the chlorination of dihydroheterocycles with phosphorus oxychloride ($POCl_3$) usually gives oxidized chloroheterocycles but not chlorodihydroheterocycles.[3h] For instance, the $POCl_3$ chlorination of dihydropyrazinones **40** (R=C_6H_5) or dihydropyridazinone **41** afforded chloropyrazines **42** or monochloropyridazine or dichloropyridazine **43** and **44**, respectively (eqs. 20, 21).[41] Folkers and Johnson[42] reported that the chlorination of dihydropyrimidines **45** (R^6=H) with $POCl_3$ did not yield the desired dihydropyrimidine derivative, while Khanina reported that the chlorination of *N*-1 methylated dihydropyrimidines **45** (R^6=Me) with $POCl_3/PCl_5$ gave oxidized pyrimidinone **46** and chloropyrimidine **47**, but not chlorodihydropyrimidine (eq. 22).[43] Doehner reported that the chlorination of dihydropyridine **48** with $POCl_3$ afforded the chloropyridine **49** due to the spontaneous air oxidation or the successive chlorination



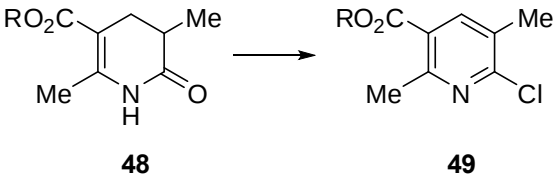
(eq. 20)



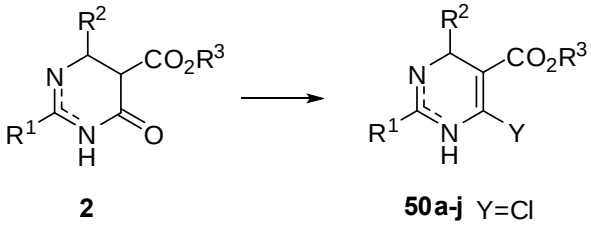
(eq. 21)



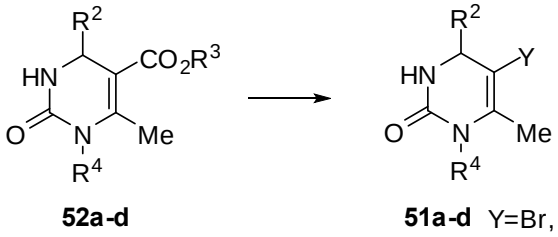
(eq. 22)



(eq. 23)



(eq. 24)



(eq. 25)

Scheme 6. Halogenation of various dihydroheterocycles

and dehydrochlorination (eq. 23).[44] However, Cho and Ueda reported the first successful $POCl_3$ chlorination at the 6-position of 4,5-dihydropyrimidin-6(1*H*)-ones **2a-i** (R^1=Me, NMe_2, C_6H_5; R^2=C_6H_5,

substituted C_6H_5, 2-furyl, 2-thienyl; R^3=Et) (eq. 24). Thus, a series of chlorodihydropyrimidines **50a-i** were obtained in 27-87% yields.[3d] Recently, Yasui and Kobayashi have synthesized ethyl 6(4)-chloro-2-methyl-4(6)-phenyl-1,4(6)-dihydropyrimidine-5-carboxylate **50j** by the chlorination of the corresponding ketone with $POCl_3$ or phenylphosphonic dichloride ($C_6H_5P(O)Cl_2$) at 110 °C in 60% yield.[3k] On the other hand, Zych and coworkers reported a new procedure of introducing a halogen atom into a dihydropyrimidin-2-one skeleton at the 5-position (eq. 25). Namely, they obtained 6-methyl-4-phenyl-5-halo-3,4-dihydropyrimidin-2(1*H*)-ones **51a-d** (Y=Br, I; R^2=4-ClC_6H_5, 4-$OMeC_6H_5$, benzyl, cyclohexyl; R^4=H) by the halodecarboxylation of carboxylic acids **52a-d** (R^2=4-ClC_6H_5, 4-$OMeC_6H_5$, benzyl, cyclohexyl; R^3=H; R^4=H) with *oxone* (monopersulfate compound: $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) and NaI/$Na_2CO_3$ in aqueous MeOH.[45]

(4) Hydrolysis and Hydrogenolysis

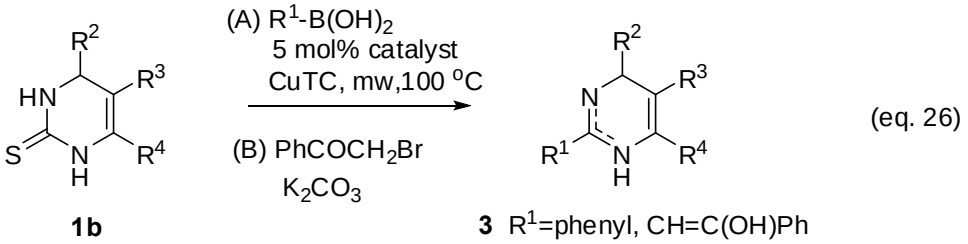
The hydrolysis of the esters **3**, **50**, and **52** was not easily achieved (Scheme 3 and 6).[1c,2a,27] For example, Zigeuner showed that *N*-1 methylated dihydropyrimidin-2-one **52a** (R^4=Me) was hydrolyzed with an aqueous base to a carboxylic acid derivative, but not the *N*-1 unsubstituted compound **52b** (R^4=H) (eq. 25).[46] The hydrolysis of benzyl ester **52c** (R^3=Bzl) was accomplished in excellent yield using $AlCl_3$ in CH_2Cl_2 at 0 °C to room temperature.[45] Also, the hydrogenolysis of benzyl ester **52c** with H_2/Pd-C in EtOH at room temperature[20] and the treatment of **52c** with iodotrimethylsilane in $CHCl_3$ at 60 °C were used for debenzylation.

(5) Liebeskind-Srogl, Eschenmoser, and Suzuki-Miyaura Cross-Coupling Reactions

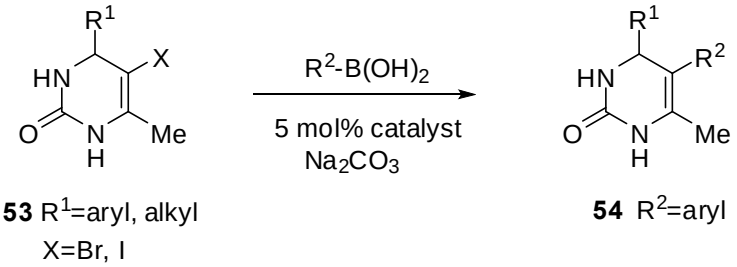
The transformation from the Biginelli-type dihydropyrimidine **1b** to the Traube-Schwarz-type dihydropyrimidine **3** was undertaken by Kappe and coworkers. The direct microwave-assisted Pd(PPh_3)$_4$-catalyzed/CuTC(copper(I) thiophene-2-carboxylate)-mediated Liebeskind-Srogl C-C cross-coupling reaction[2o] of 3,4-dihydropyrimidine-2-thiones **1b** (X=S; R^2=aryl; R^3=CO_2R; R^4=Me) with boronic acids led to various forms of 1,4(1,6)-dihydropyimidine **3** (R^1=Ph, 2-phenylvinyl; R^3=CO_2R; R^4=Me) in 14-82% yields.[2i,l,o] Similarly, they obtained benzoyldihydropyrimidine **3** (R^1=C_6H_5; R^2=aryl; R^3=COC_6H_5; R^4=Me) from thiolester **1c** (X=S; R^3=COSEt; R^4=Me) (Scheme 7, eq. 26).[2k] Eschenmoser coupling reactions of **1b** with α–bromoacetophenone in the presence of K_2CO_3/acetone were independently carried out at the same time by the groups of Wyatt[26] and Singh[37] to provide 2-substituted-vinyldihydropyrimidines **3** (R^1=CH=C(OH)Ph; R^2=aryl; R^3=CO_2R; R^4=Me) (eq. 26) in 80% yield. The Suzuki-Miyaura cross-coupling reaction on a dihydropyrimidine ring was reported by Zych.[45] The cross-coupling reaction at the 5-position of dihydropyrimidines **53** (X=Br, I) with organoboronic acids in the presence of 5 mol% $Pd_2(dba)_3$, Pd(*t*-$Bu_3P)_2$, or $PdCl_2$(dppf) and a base (Na_2CO_3, NaOBu-*t*, or KF) provided 6-methyl-4-phenyl-5-substituted-3,4-dihydropyrimidine-2(1*H*)-ones **54** from

5-halodihydropyrimidines **53** (R^1=C_6H_5, 4-ClC_6H_5, 4-$OMeC_6H_5$, benzyl, cyclohexyl; R^2=C_6H_5, *m*-, *p*-MeC_6H_4, *m*-, *p*-$OMeC_6H_4$, 2-naphtyl, 2-phenylvinyl) in 46-92% yield (eq. 27). However, sterically hindered or electron-deficient organoboronic acids (R^1=C_6H_5; R^2=*o*-MeC_6H_4, *p*-FC_6H_4) gave generally inferior results. At the same time, Yasui and Kobayashi developed the Suzuki-Miyaura cross-coupling reaction at the 4-position of dihydropyrimidine **55** (X=Cl) (see the section of *N*-alkoxycarbonylation) with organoboronic acids or triethylborane in the presence of Pd catalysis, although the reaction of **3** (R^3=CO_2Et) with organoboronic acids did not work out.[3k] The reaction of **55** and organoboronic acids or Et_3B in the presence of 5 mol% bis(triphenylphosphine)palladium (II) dichloride: $PdCl_2(PPh_3)_2$ and Cs_2CO_3 in DMA at 60 °C provided **56** (R^1=C_6H_5; R^2=C_6H_5, *o*-MeC_6H_4, *o*-$OMeC_6H_4$, 2-phenylvinyl, 3-thienyl, Et) in 85-99% yield. However, electron-deficient organoboronic acid afforded **57** (R^1=C_6H_5; R^2=*p*-$NO_2C_6H_4$) in 69% yield (eq. 28).

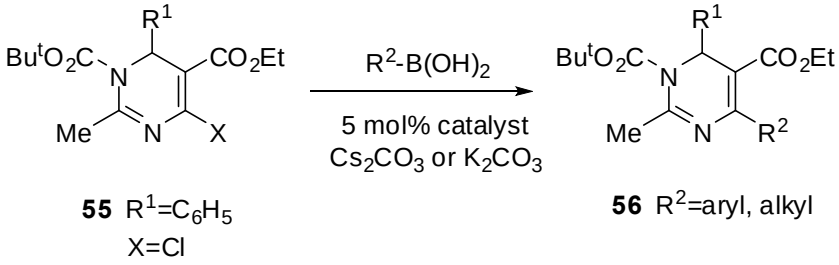
The cross-coupling reactions at the 2-, 4- and 5-positions should be useful because they might be applied to synthesize other dihydropyrimidines with various functional groups at all positions.



(eq. 26)



(eq. 27)

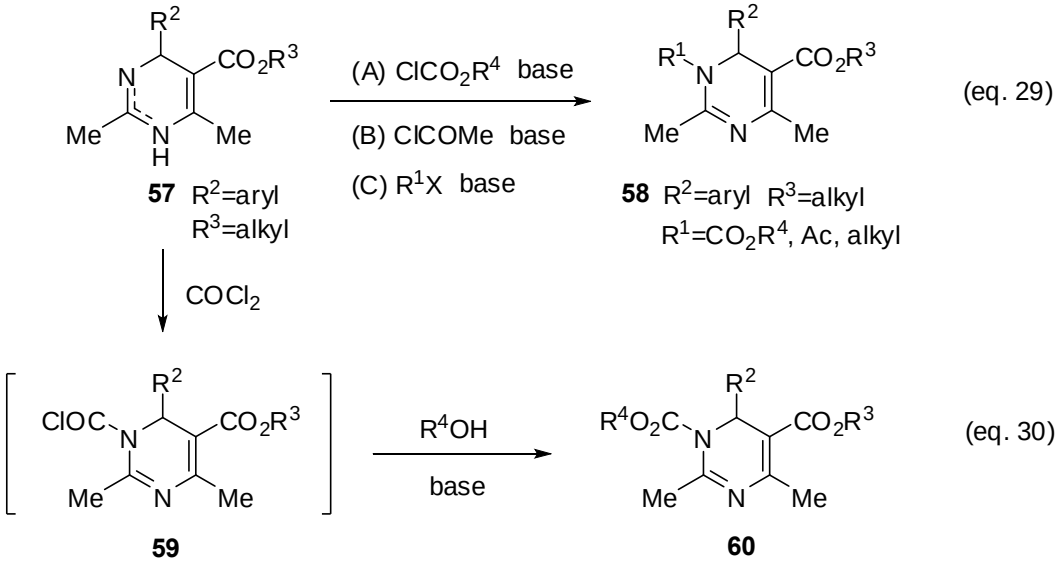


(eq. 28)

Scheme 7. Cross-coupling reaction at the 2, 4, or 5-position of dihydropyrimidines

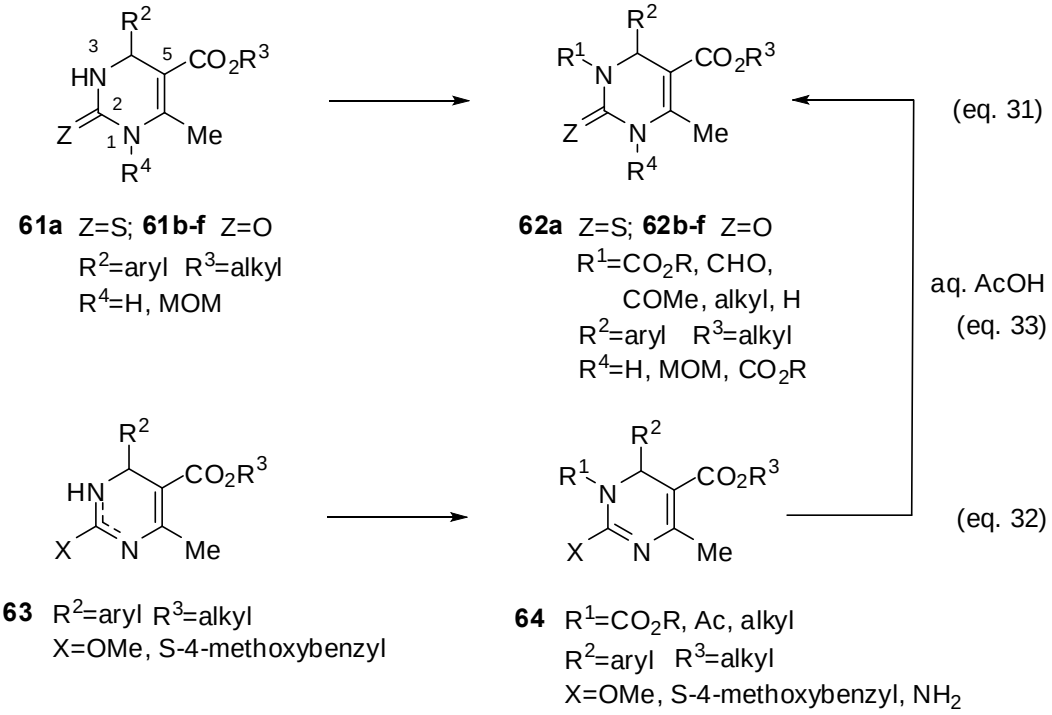
(6) *N*-Alkoxycarbonylation, *N*-Acylation, and *N*-Alkylation

Novel methods of regiospecific *N*-alkoxycarbonylation, *N*-acylation, and *N*-alkylation of dihydropyrimidines **57** for obtaining pharmacologically active compounds, calcium antagonists, were discovered in 1985 by Cho and coworkers (Scheme 8).[3c] The reactions of sodium salts of **57** with alkyl chloroformate ($ClCO_2R^4$) or acyl chloride (R^5=Me, cyclopropyl) regiospecifically yielded a single compound, **58** (R^3=Et, cyclopropylmethyl; R^4=Me, Et, $(CH_2)_2OMe$), in good to excellent yields. Similarly, **58** (R^1=Me, *n*-C_7H_{15}) was obtained from the alkylation of its sodium salts of **57** and alkyl halide (MeI, $C_7H_{15}I$)/HMPA in moderate yields (eq. 29). The finding of the regiospecificity could be rationalized in two ways. First, the nitrogen atom at the 3-position may be less sterically hindered since the DP ring can be assumed almost perpendicular to the phenyl ring. Secondly, if one draws the possible resonance structures of the anion that would result from the removal of a proton from the nitrogen of **57**, it is clear that *N*-3 should bear a higher electron density than *N*-1 and therefore should be more nucleophilic.[3c] To obtain dihydropyrimidines with a complicated alkoxycarbonyl group or a nitrogen-containing alkoxycarbonyl group at the 1-position, the *N*-alkoxycarbonylation of **57** with trichloromethyl chloroformate (phosgene dimer) was performed.[3f] Thus, without isolating, the resulting unstable intermediate **59** was treated with alcohol (R^4OH) or aminoalcohol to provide the compounds **60** (R^1=*o*- or *m*-$NO_2C_6H_4$, 2-3-$Cl_2C_6H_3$; R^3=*i*-Pr, cyclopropylmethyl; R^4=$(CH_2)_2$-2-pyridyl, $(CH_2)_2N(Bzl)(CH_2)_3Ph$, etc.) in good yields (eq. 30).[3f]



Scheme 8. Regiospecific *N*-alkoxycarbonylation, *N*-acylation, and *N*-alkylation of 1,4(1,6)-dihydropyrimidine **57**

On the other hand, the *N*-alkoxycarbonylation of Biginelli dihydropyrimidines **61** did not regiospecifically give the desired *N*-3 substituted compounds **62** as will be described later (Scheme 9, eq. 31).[3a] Therefore, Atwal and coworkers synthesized a series of *N*-3-substituted dihydropyrimidines **62**[4c,d] via **63** and **64** to synthesize pharmacologically active compounds according to the cyclization procedure[3c] (eq. 32). Thus, dihydropyrimidines **64a** (X=OMe) and **64b** (X=S-*p*-methoxybenzyl) were obtained in good yields, for comparison with the dihydropyridines, calcium antagonists.[4c-e] The deprotection of **64b** (X=S-*p*-methoxybenzyl) was accomplished by treatment with an aqueous acid to furnish a series of **62** (R^1=CO_2Et etc; R^2=$NO_2C_6H_4$, ClC_6H_4, $CF_3C_6H_4$; R^3=Et, *i*-Pr; R^4=H; Z=O, S) (eq. 33).[4d] They found a potent compound, **62a** (R^1=CO_2Et; R^2=*m*-$NO_2C_6H_4$; R^3=*i*-Pr; R^4=H; Z=S), among them.[4d-g] Only a few studies on the synthesis of optically active compounds were reported.[11k] Atwal and Rovnyak obtained the optically active enantiomers **63a** and **65b** by transformation from **63a**, as shown in Scheme 10.[4e,f] Consequently, the compound **63a** was converted to the diastereomeric ureas **66a** and **66b** by a two-step procedure involving the treatment of **63a** with *p*-nitrophenyl chloroformate followed by the reaction of the resulting intermediate with (*R*)-(-)-α-methylbenzylamine **67** (eq. 34). The diastereomers **66a** and **66b** were separated by crystallization. The cleavage of the urea group was performed by treatment with DBU to yield the enantiomers **68a** and **68b**, which were transformed via **69** to yield **65a** and **65b**, respectively. The absolute stereochemistry of **65a** was confirmed by single-crystal X-ray analysis.



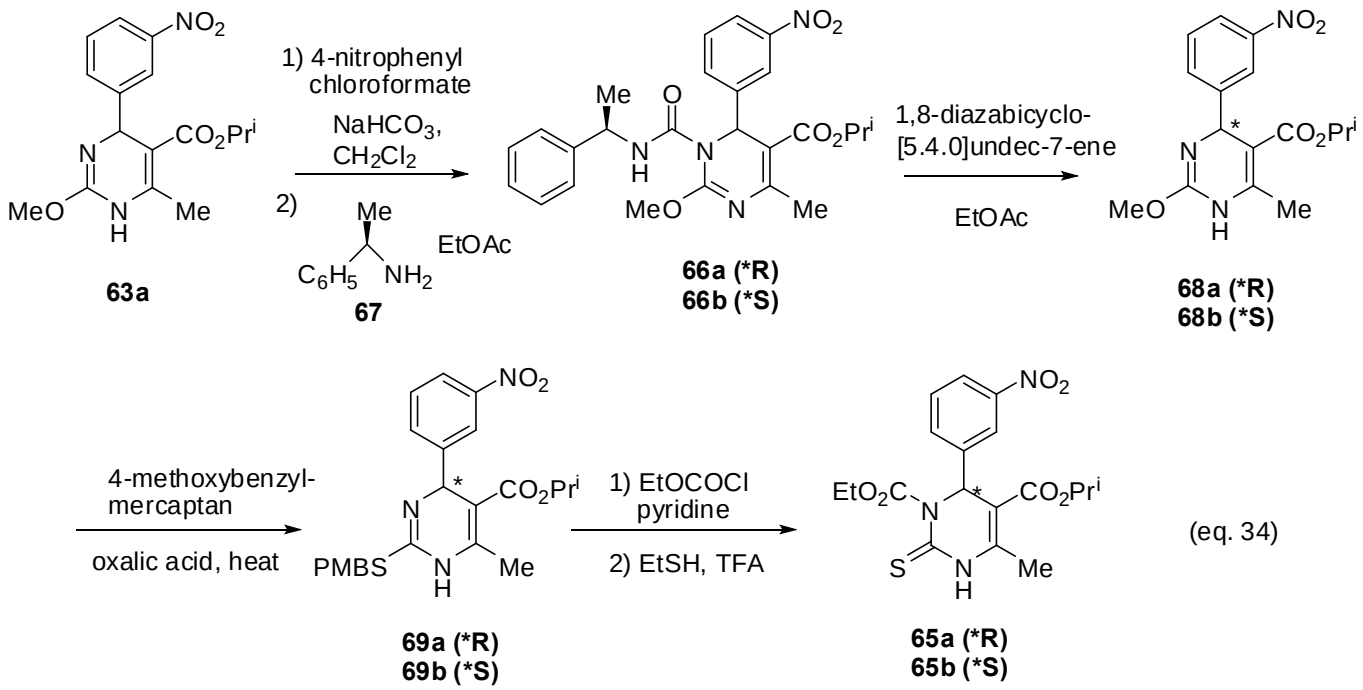
61a Z=S; **61b-f** Z=O
R^2=aryl R^3=alkyl
R^4=H, MOM

62a Z=S; **62b-f** Z=O
R^1=CO_2R, CHO, COMe, alkyl, H
R^2=aryl R^3=alkyl
R^4=H, MOM, CO_2R

63 R^2=aryl R^3=alkyl
X=OMe, S-4-methoxybenzyl

64 R^1=CO_2R, Ac, alkyl
R^2=aryl R^3=alkyl
X=OMe, S-4-methoxybenzyl, NH_2

Scheme 9. Regioselective *N*-alkoxycarbonylation, *N*-acylation, and *N*-alkylation of Biginelli dihydropyrimidine **61**



Scheme 10. Resolution of dihydropyrimdine **63**

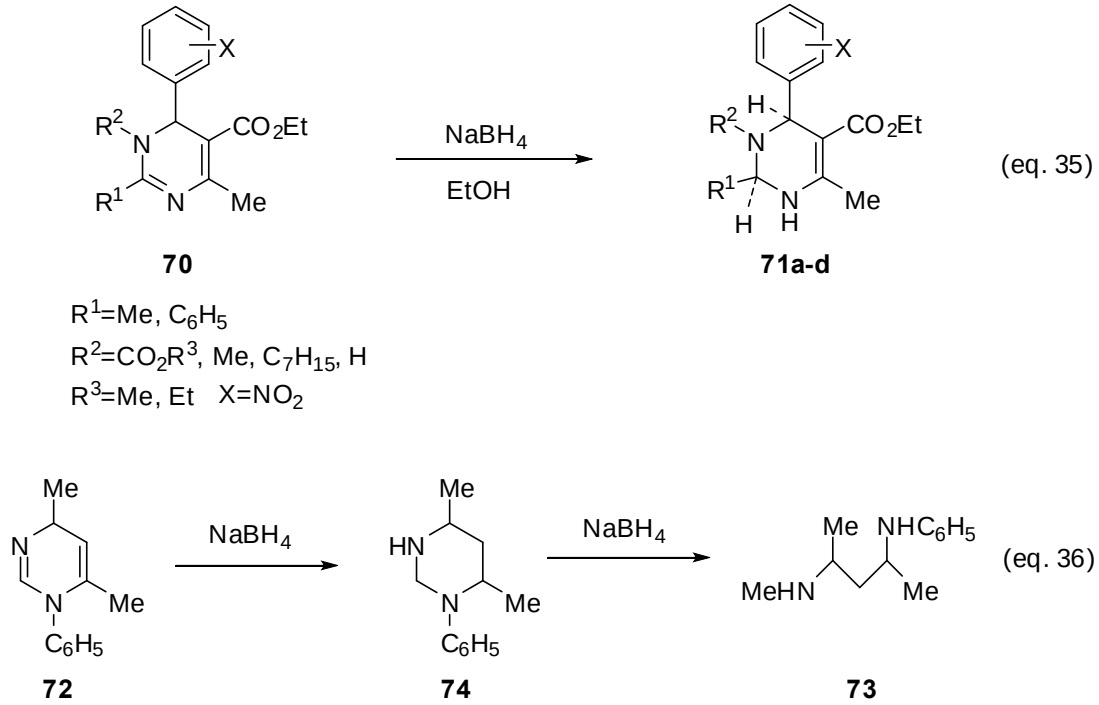
As for the reactions of Biginelli dihydropyrimidine, **61b** (R^2=aryl; R^4=H; Z=O) was alkylated regioselectively at the *N*-1 position when treated with alkyl halide in the presence of a suitable base (Scheme 9).[3a,47] On the other hand, the *N*-acetylation and *N*-formylation of **61b** with acetic anhydride[2c,42b] and DMF/$POCl_3$[2c] occurred at the *N*-3 position to give the compounds **62b** (R^1=Ac; R^4=H; Z=O) and **62c** (R^1=CHO; R^4=H; Z=O), respectively. As for the *N*-alkoxycarbonylation of **61** (R^4=H; Z=O), Cho and coworkers reported that the regioselectivity of the products depended on the position (*ortho*, *meta*) of the substituent on the aromatic ring (R^2) of **61**. Namely, *ortho*-substituted compounds resulted in *N*-1 alkoxycarbonylation, because of the steric hindrance of a nitro group (eq. 31).[3a] To the contrary, the *N*-alkoxycarbonylation of *meta*-substituted compounds (R^2=*m*-$NO_2C_6H_4$; R^3=Et; R^4=H; Z=O) with NaH/$ClCO_2Et$ (or $ClCO_2C_7H_{15}$-*n*) afforded *N*-3-substituted dihydropyrimidines **62d** and **62e** (R^1=CO_2Et, R^1=$CO_2C_7H_{15}$-*n*; R^2=*m*-$NO_2C_6H_4$; R^3=Et; R^4=H; Z=O) in 80-99% yield as a single compound, while the reaction of **61** (R^2=*o*-$NO_2C_6H_4$; R^3=Et; R^4=H; Z=O) yielded the *N*-1-substituted compounds **62f** (R^1=H; R^2=*o*-$NO_2C_6H_4$; R^3=Et; R^4=$CO_2C_7H_{15}$-*n*; Z=O) in 10% yield with the recovery of **61f**. To obtain the *N*-3-substituted compound **62e** with *o*-NO_2 derivatives, protection with a methoxymethyl (MOM) group at the 1-position of **61e** (R^2=*o*-$NO_2C_6H_4$; R^3=cyclopropylmethyl; R^4=H; Z=O) was effective. Thus, the compound **62e** (R^1=$CO_2C_7H_{15}$-*n*; R^2=*o*-$NO_2C_6H_4$; R^3=cyclopropylmethyl; R^4=H; Z=O) was provided in 40% yield (3 steps) from **61e** after protection with the MOM group, alkoxycarbonylation and the removal of the MOM group with an aqueous acid.[3a]

(7) Oxidation

Dihydropyrimidines are sometimes spontaneously oxidized during SiO_2 column chromatograpy or storage. The reported method for the chemical oxidation of 4-substituted-1,4(1,6)-dihydropyrimidine **3** utilizes mainly transition-metal-based oxidizing agents, such as $Mn(OAc)_3$,[48] MnO_2,[2g] $(NH_4)_2Ce(NO_3)_6$,[2g] and $CuCl_2/Na_2CO_3$/*t*-BuOOH.[49] The dichlorodicyanoquinone (DDQ, benzene, reflux, 1h) oxidation of 6(4)-chloro-1,4(1,6)-dihydropyrimidine **3** (R^1=C_6H_5; R^2=*p*-$SMeC_6H_4$; R^3=Et; X=Cl) furnished the corresponding pyrimidine in 88% yield, but **3** (R^1=NMe_2; R^2=*m*-$NO_2C_6H_4$; R^3=Et; X=Cl) gave the pyrimidine in 38% yield.[3d] Recently, mild and efficient oxidation of 2-methylthio-4-alkyl- or 4-aryl-1,4-dihydropyrimidines **3** with (diacetoxyiode)benzene: $PhI(OAc)_2$ has been reported.[40] Also, an efficient aerobic oxidative dehydrogenation of 4-substituted dihydropyrimidinones **1** and dihydropyrimidines **3** was performed to give the corresponding pyrimidinones and pyrimidines, respectively, in high yields by molecular oxygen (1 atm) in the presence of catalytic amounts of *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2$.[27]

(8) Reduction

Various methods of reduction to furnish 1,4(1,6)- and 2,5-dihydropyrimidines from pyrimidines were described above (Scheme 4, eqs. 14-17). However, only a few examples exhibit the reduction from a dihydropyrimidine to a tetrahydropyrimidine. In the case of having an *N*-alkoxycarbonyl substitute at the 3-position as **70**, the reduction of **70** hydrochloride (prepared with anhydrous HCl/Et_2O in MeOH) with

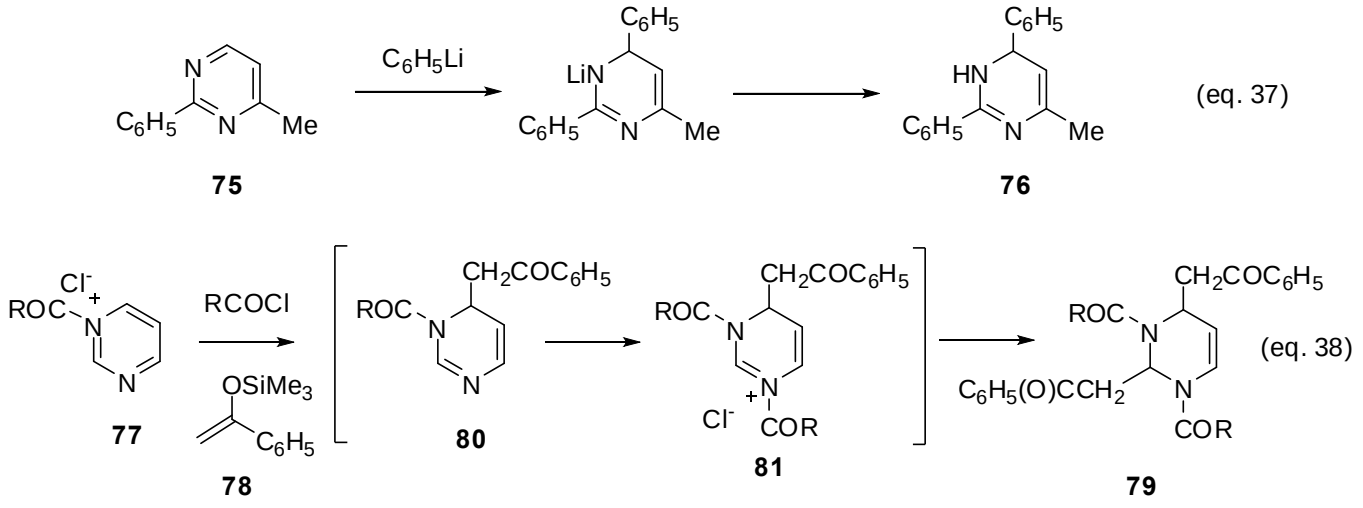


Scheme 11. Reduction of dihydropyrimidines

2 mol equivalents of $NaBH_4$ at room temperature for 0.5 h quantitatively furnished the corresponding tetrahydropyrimidine **71a** (X=*o*-NO_2, R^1=Me, R^2=CO_2Et) or **71b** (X=*o*-NO_2, R^1=C_6H_5, R^2=CO_2Me) as the sole compound (Scheme 11, eq. 35).[3c] The stereochemistry of **71a** was determined as a *cis* stereoisomer by X-ray crystallographic analysis. In the case of the acyl compound **70** (R^1=Me, R^2=COMe), the $NaBH_4$ reduction gave a complex mixture. However, in the case where *N*-3 was unsubstituted or alkyl-substituted, the reduction afforded a 1:1 or 4:1 mixture (the major isomer was *cis* by an NOE) of stereoisomeric tetrahydropyrimidines **70c** (X=*m*-NO_2, R^1=Me, R^2=H) or **70d** (X=*o*-NO_2, R^1=Me, R^2=*n*-C_7H_{15}) in each case. On the other hand, Kashima and coworkers performed the reduction of 1,4-dihydro-4,6-dimethyl-1-phenylpyrimidine **72** with a large excess of $NaBH_4$ in EtOH at room temperature for 24 h and obtained 4-anilino-2-methylaminopentane **73** via hexahydropyrimidine **74** (eq. 36).[12h]

(9) Nucleophilic Addition and Nucleophilic Substitution

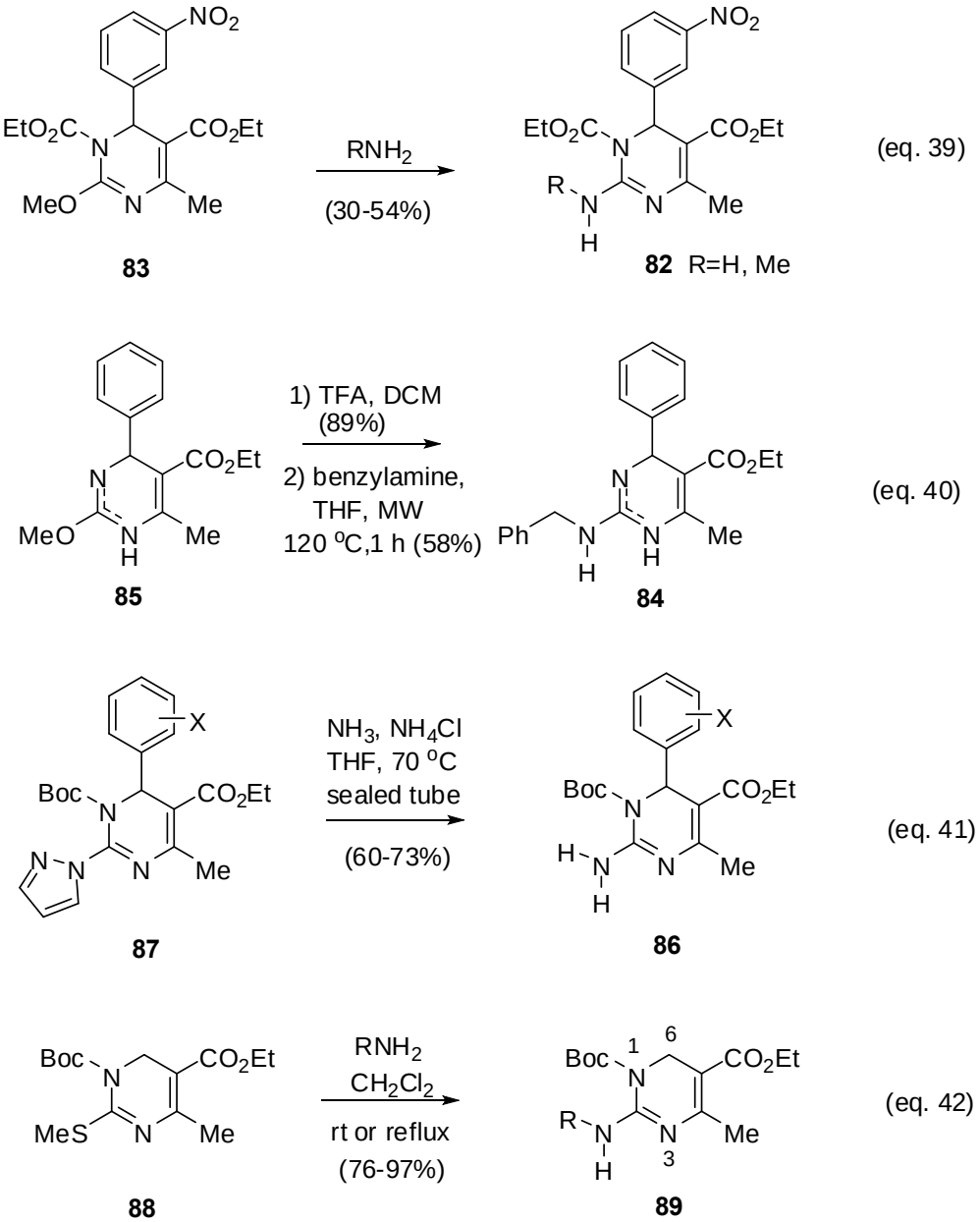
Heyes reported that the reductive nucleophilic addition at the 6-position of 4-methyl-2-phenylpyrimidine **75** with phenyllithium provided 4-methyl-2,6-diphenyl-1,6-dihydropyrimdine **76** (eq. 37).[8] Akiba and coworkers observed that the reaction of pyrimidine **77** quarternized with acetyl chloride (1 mol equivalent) and trimethylsilyl ether **78** (1 mol equivalent) of enolic acetophenone afforded 1,2,3,4-tetrahydropyrimidine **79** in 48% yield as a mixture of diastereoisomers without the 1:1 adduct **80** (eq. 38).[50]



Scheme 12. Nucleophilic addition at the 2- and 6-positions of pyrimidine rings

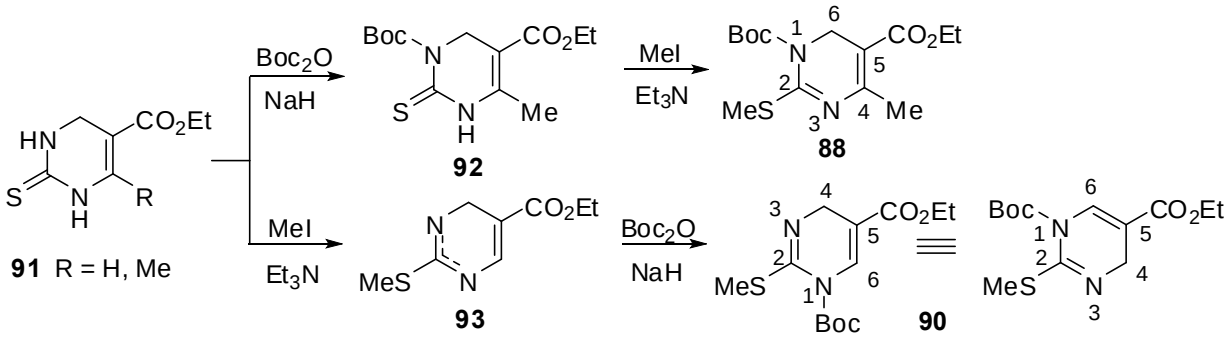
The reactivity at the 2-position of dihydropyrimidines is quite different from that of pyrimidines. In fact, compared with well-known nucleophilic substitutions of pyrimidines having a leaving group at the 2-position,[2g,51-54] those of dihydropyrimidines are rare because of the low reactivity of

dihydropyrimidines at the 2-position. Actually, Kwon's theoretical study revealed that the LUMO energy level of dihydropyrimidines such as 2-chlorodihydropyrimidine-5-carboxylic acid was higher at about 11.8-17.5 kcal/mol than that of 2-chloropyrimidine-5-carboxylic acid. This high-lying LUMO energy level of dihydropyrimidines induced a barrier for attack by the HOMO of nucleophiles such as aniline.[3j] Thus, only a few studies on the substitution at the 2-position of 4-phenyldihydropyrimidines have been reported.[2g,4c,d,55,56] Moreover, the yields are not always satisfactory. Namely, Atwal reported the synthesis of 2-amino-4-(3-nitro)phenyldihydropyrimidines **82** (Scheme 12, eq. 39) in 30-54% yield by aminolysis with NH_3 or $MeNH_2$ at the 2-position of 1,4(3,4)-dihydropyrimidines **83**.[4c,d] Kappe obtained



Scheme 13. Nucleophilic substitution at the 2-position of dihydropyrimidines

2-benzylamino-1,4-dihydropyrimidine **84** in 58% yield by the microwave irradiation of a mixture of the 2-methylthio-1,4-dihydropyrimidine **85** TFA salts in DCM and benzylamine at 120 °C (eq. 40).[2g] Overman reported the synthesis of 2-aminodihydropyrimidine **86** (X=H, *m*-NO_2) in 75-77% yield by aminolysis (NH_3–NH_4Cl, 70 °C, 12 h, in a sealed tube) with **87** having a pyrazole moiety at the 2-position (eq. 41).[56b] Recently, Nishimura and Yasui have found more effective procedures in which the nucleophilic substitution at the 2-position of 2-methylsulfanyl-1,6-dihydropyrimidine-1,5-dicarboxylate **88** with aromatic or aliphatic primary amines (aniline, 4-methoxyaniline, 4-methoxycarbonylaniline, benzylamine, *n*-hexylamine, *O*-benzylhydroxylamine, *etc.*) provided a variety of 6-unsubstituted-2-amino-1,6-dihydropyrimidines **89** in 76-97% yield (eq. 42).[3j] The deprotection of a Boc group in a series of compounds **89** was quantitatively performed using TFA. Interestingly, in contrast to **88**, the other compound **90** protected at the 1-position with a Boc group gave no substituted dihydropyrimidines (eq. 42) except ring-cleaved compounds, as will be described later. The methods of synthesizing **88** and **90**



(eq. 43)

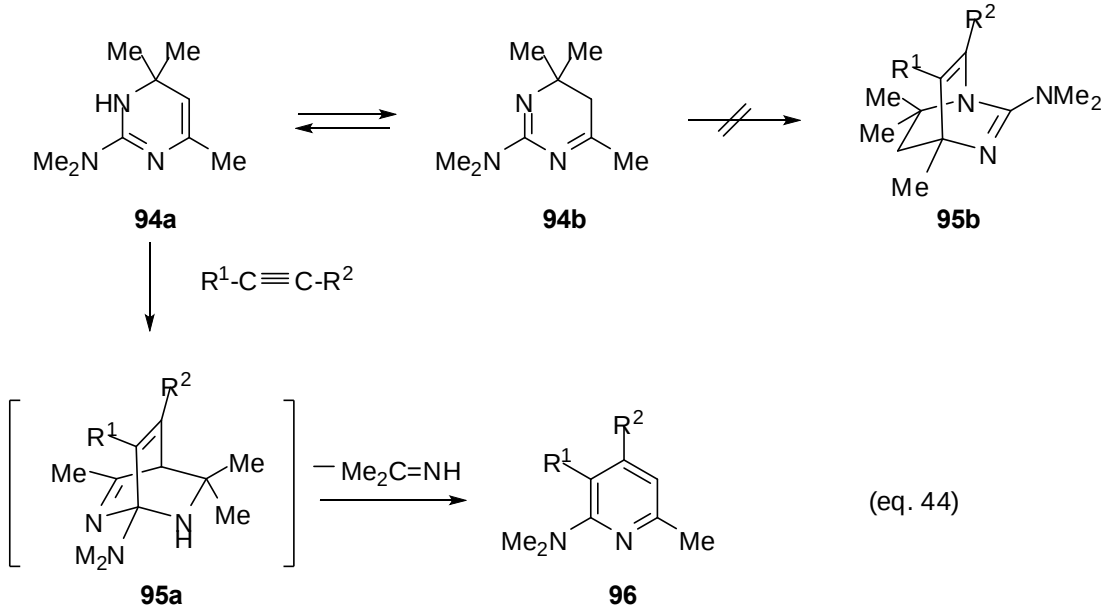
Scheme 14. Preparation of 1-*N*-substituted 1,4- and 1,6-dihydropyrimidines

from **91** were somewhat tricky because a Boc group was regioselectively introduced at the different positions in **90** and **92**. Consequently, the compounds were provided via intermediates **92** and **93**, respectively (Scheme 14).

(10) Ring Cleavage

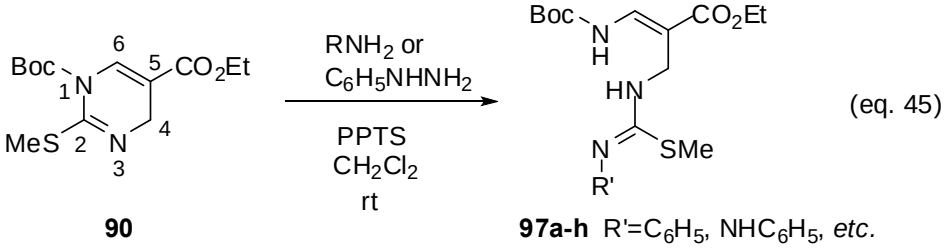
Generally, most heterocyclic rings cannot be easily cleaved and so only a few studies on them have been reported.[12i,57,58] For instance, Maddaluno reported that treating *N*-substituted pyrrolidines and piperidines bearing an allylic chain α to nitrogen with strong bases led to the opening of a heterocycle and provided 1,3-dienes disubstituted with an alkoxy and an aminoalkyl chain.[57] Kashima and Omote described the ring-cleavage of 1,4-dihydro-4,6-dimethyl-1-phenylpyrimidine **72** with a large excess of $NaBH_4$ in Scheme 11 (eq. 36).[12h] A novel method of the [4+2]cycloaddition of 1,6-dihydro-2-dimethylamino-4,6,6-trimethylpyrimidine **94** as azadienes with acetylenic compounds was also reported by Kashima and Shimizu.[12i] In this method, the cycloaddition of **94** with dimethyl acetylenedicarboxylate in benzene at

room temperature took place across the C-2 and C-5 carbons to furnish the [4+2]adduct **95a**, although it was not detected. Retro-cycloaddition also took place with the loss of 2-iminopropane to afford the 2-dimethylaminopyridine derivative **96** with aromatization in 61% yield. Although the dihydropyrimidine **94** consisted of tautomeric mixtures of **94a** (1,6-DP) and **94b** (4,5-DP), the reaction proceeded via **95a** from the tautomer **94a** (enamine-DP) but not the other unstable tautomer **94b** (imine-DP), because **94b** should give the intermediate **95b**.



Scheme 15. Cleavage of the dihydropyrimidine ring; the [4+2]cycloaddition of the dihydropyrimidine with acetylenic compounds

Cho and Yamaguchi observed that the nucleophic addition of 4,6-unsubstituted-1,4-dihydropyrimidine **90** with an aniline derivative or phenylhydrazine in the presence of pyridinium *p*-toluenesulfonate (PPTS) resulted in a ring cleavage between the 1- and 2-positions of the 1,4-dihydropyrimidine skeleton to furnish the compounds **97a-f** (R'=C_6H_5, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-MeC_6H_4, *m*,*p*-$(MeO)_2C_6H_3$, NHC_6H_5) in 65-95% yield (**97g-h**; except *o*-MeC_6H_4 and NHC_6H_5 each in 24%),[31] although the nucleophilic substitution of 4-methyl-6-unsubstituted-1,6-dihydropyrimidine **88** with the same amines furnished



Scheme 16. Ring cleavage of 4,6-unsubstituted 1,4-dihydropyrimidine

conventional substituted products **89** at the 2-position in excellent yields.[3j]

The reactions were limited to those of the aniline derivatives above or phenylhydrazine, because aralkylamines, alkylamines, or heterocyclic amines did not cleave the skeleton. The ring-opening chemical structure of **97a** (R'=C_6H_5) was confirmed by X-ray crystallographic analysis.

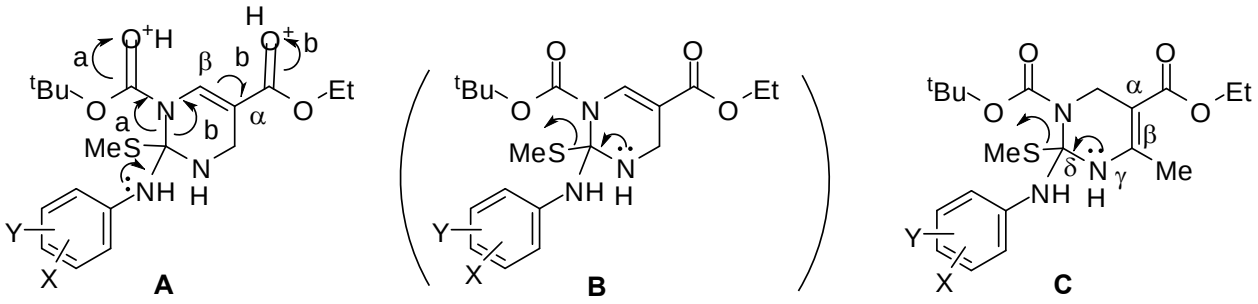


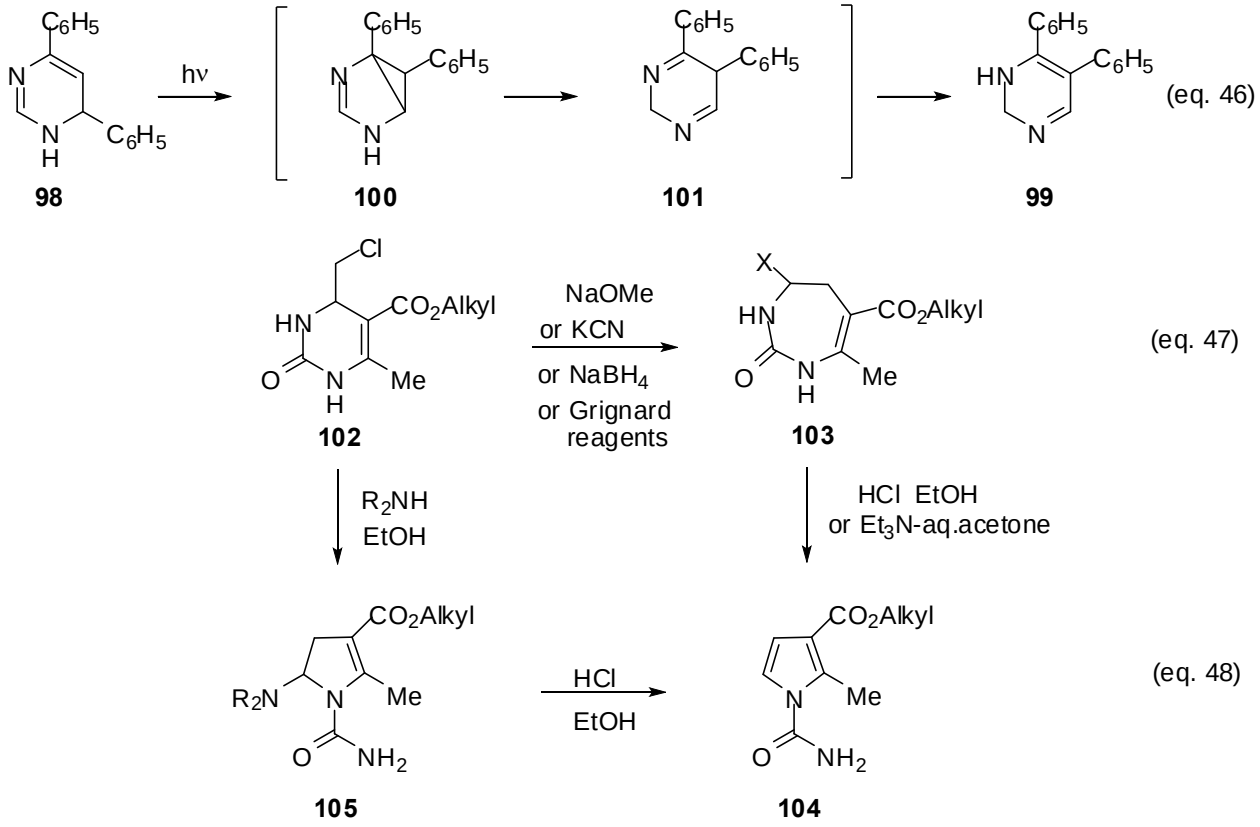
Figure 8. Reaction mechanism by the effect of an α,β–unsaturated ester group and/or a Boc group

The reaction proceeded not as in **B** but as in **A** (Figure 8) to yield the ring-opening compound **97**, presumably by the effect of an α,β-unsaturated ester group and a Boc group. On the other hand, it is assumed that, in the case of reactions of **88** with amines, elimination occurred to afford **89** (eq. 42) so that the product shown in **C** in Figure 8 generated α,β- and γ,δ-conjugated double bonds.[3l]

(11) Rearrangement

Only a few reports have been made on the rearrangement of a dihydropyrimidine ring. In particular, van der Plas discovered the di-π-methane photochemical rearrangement from 4,6-diphenyl-1,6-dihydropyrimidine **98** to 5,6-diphenyl-1,2-dihydropyrimidine **99**.[59] There are two interconversion between 1,4-, 1,6-, and 4,5-dihydropyrimidines and between 1,2- and 2,5-dihydropyrimidines (Figure 2). Although thermal interconversion between two groups was not observed, the photochemical rearrangement of 1,4(1,6)-dihydropyrimidine to 1,2-isomers was observed. The rearrangement should include 2,4-diazabicyclo[3.1.0]hex-2(3)-ene **100**, after the successive cleavage of the three-membered ring with a concomitant homo[1,5]hydrogen shift from nitrogen to carbon at the 2-position yielded the imine **101**, which isomerized to a rearranged enamine **99** (eq. 46). However, the isolation of **99** failed because of its instability. Therefore, evidence of its existence was only based on spectral and chemical data.

The reaction of 4-chloromethyldihydropyrimidine **102**[60a] with nucleophilic reagents (NaOMe, KCN, $NaBH_4$, and Grignard reagents) caused ring cleavage to afford 2,3,6,7-tetrahydro-2-oxo-1*H*-1,3-diazepine-5-carboxylates **103** (X=OMe, CN, H, alkyl, aryl) in high yields.[60a,b,61-64] Some compounds



Scheme 17. Rearrangement of a dihydropyrimidine ring

were converted into 1-carbamoylpyrrole **104** under acidic[61] or basic condition.[60a] On the other hand, the treatment of **102** with a secondary amine provided **105**,[60a] which was transformed under acidic condition to 1-carbamoylpyrrole **104**.

V. VARIOUS SKELETONS DERIVED FROM MONOCYCLIC DIHYDROPYRIMIDINES

(1) Bicyclo- and Spiro-Compounds

In some cases, the reaction (eq. 6) of **9**, **10** and **11** or the cyclization (eq. 7) of α,β-unsaturated carbonyl compounds with benzamidine **12a** provided bicyclo-compounds. For instance, after the formation of a dihydropyrimidine ring, an *ortho*-OH group of a benzene ring attacked a double bond to give 2,4-diaza-6,7-benzo-8-oxabicyclo[3.3.1]nonane-2-thione **106**[20] and 1-methyl-2,4-diaza-6,7-benzo-8-oxabicyclo[3.3.1]non-3-ene **107**[111] in 79% and 90% yields, respectively (Figure 9). When a large excess of the acylating agent (2,2,2-trichloroethyl chloroformate) was used instead of ethyl chloroformate in the reaction (Scheme 12; eq. 38), 3-phenyl-8,9-bis-(2,2,2-trichloroethoxycarbonyl)-2-oxa-8,9-diazabicyclo-[3.3.1]nona-3,6-diene **108** was furnished in 29% yield from the intermediate **81**.[50] The bicyclo-compound **109** was obtained by intramolecular Michael addition of a sulfur atom (X=S) of **103** to an α,β-unsaturated carbonyl moiety.[60a,b,61]

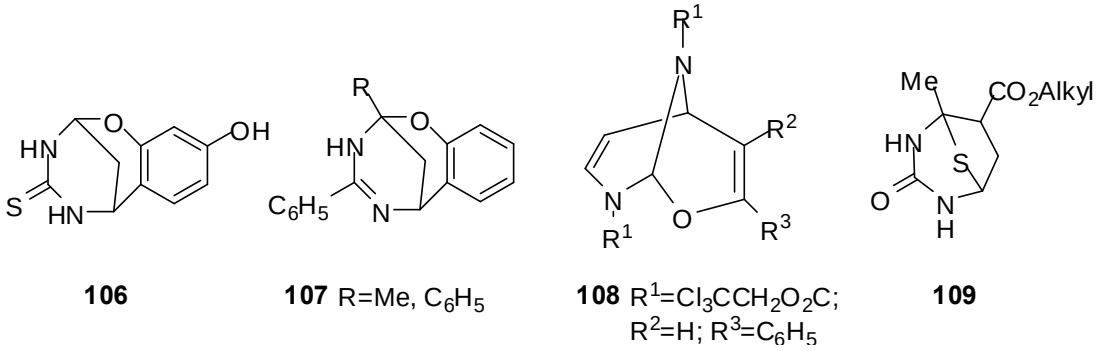
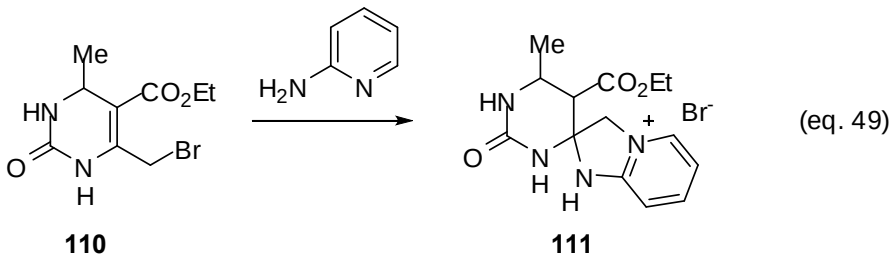


Figure 9. Bicyclo-compounds derived from dihydropyromidines

Only a few studies on the synthesis of spiro-dihydropyrimidine derivatives were reported. As shown in Scheme 18, the *N*-alkylation of 6-bromomethyldihydropyrimidine **110**[65] with 2-aminopyridine afforded the salt of pyridine nitrogen, and an amino group attacked the β-position of the α,β-unsaturated ester moiety to provide spiro-compound **111**.

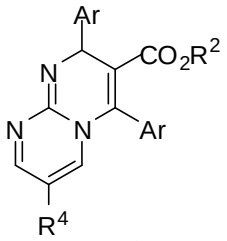


Scheme 18. Spiro-compound derived from dihydropyrimidine

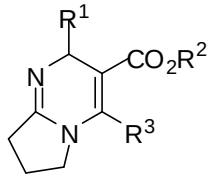
(2) Bicyclic, Tricyclic and Tetracyclic Dihydropyrimidines

Various methods of synthesizing bicyclic, tricyclic and tetracyclic dihydropyrimidines were developed by many researchers.[2-4,12,24-26,36,40,48,56,66-108] The main purpose was to stabilize monocyclic 1,4(1,6)-dihydropyrimidine skeletons and find new biologically active compounds. The synthetic procedures for multicyclic dihydropyrimidines are essentially almost the same as those for monocyclic compounds. In some cases, those compounds were synthesized by the cyclization of the functional groups of neighboring positions or by reactions with any suitable substances at a given position. Therefore, N1-C2,[2n,12g,56e,68] C2-N3,[2c,3j,3l,4h,i,48,104-108] N1-C2/C5-C6,[2m,24,25,75,79,89,95,102] N3-C4,[56] N3-C4/C5-C6,[88] C5-C6,[2h,26,36,40,70-72,76,97-99] C6-N1,[77] C4-C5/C5-C6,[56] and C2-N3/N3-C4[56,66] bonds are shared in a fused ring. Thus, bicyclic, tricyclic and tetracyclic dihydropyrimidines were synthesized as shown in Figure 10. Because of the limited space for this review, the chemical structures and compound numbers with reference numbers are simply given in Figure 10.

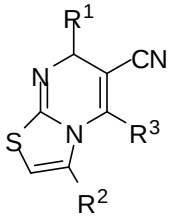
N1-C2 Bond



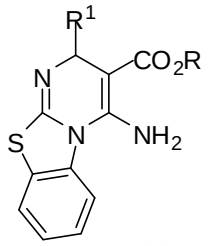
112 [2n]



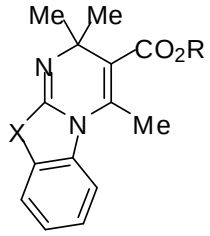
113 [2n]



114 [56e]

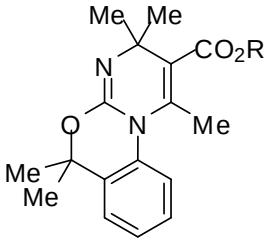


115 [68]



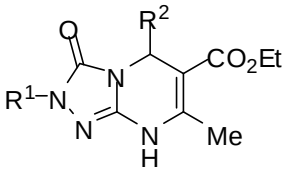
116 [12g]

X=O, S, NH

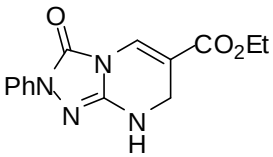


117 [12g]

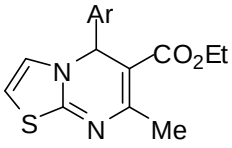
C2-N3 Bond



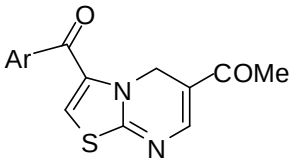
118a (R^1=Ph, R^2=H) [3j]
b (R^1=H, R^2=Ar) [4j]



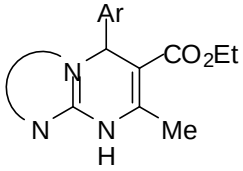
119 [3l]



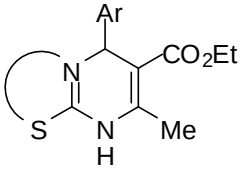
120 [104]



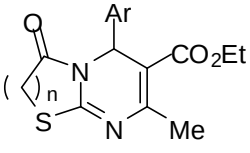
121 [105]



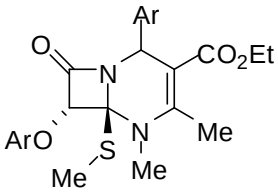
122 [4h, i]



123 [2c, 48, 106, 107]

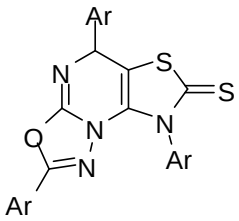


124 [2c, 48, 106, 107]

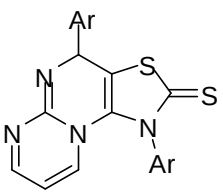


125 [108]

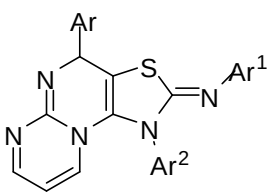
N1-C2 and C5-C6 Bonds



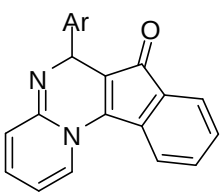
126 [75]



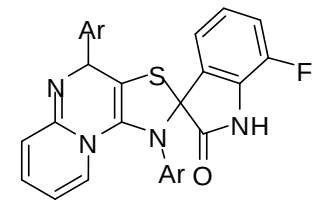
127 [75]



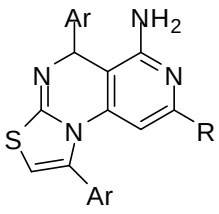
128 [24, 25]



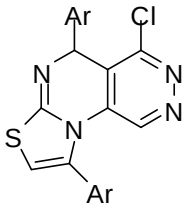
129 [2m, 75, 95, 102]



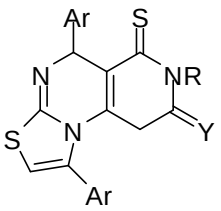
130 [89]



131 [79]

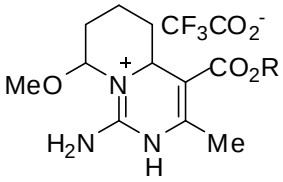


132 [79]



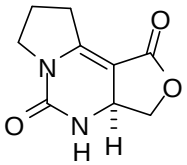
133 [79] Y=S, NH

N3-C4 Bond



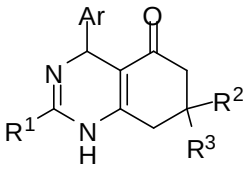
134 [56]

N3-C4 and C5-C6 Bonds



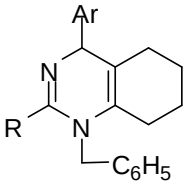
135 [88]

C5-C6 Bond



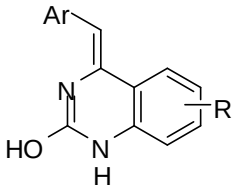
136 [36, 40, 72, 76, 97, 99]

R^1=NHAr, Ar;
R^2, R^3=H, Me, Ar

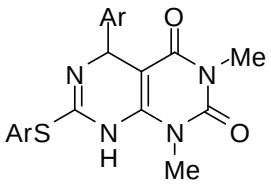


137 [26, 97]

R=OMe, NR^1R^2

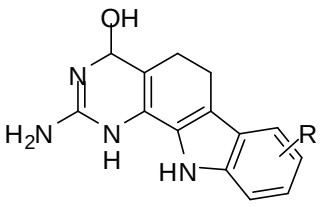


138 [2h]



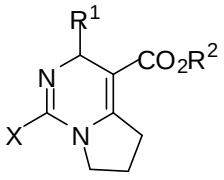
139 [98]

C5-C6 Bond



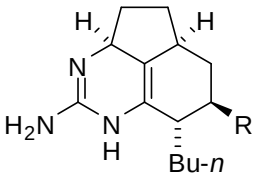
140 [70, 71]

C6-N1 Bond



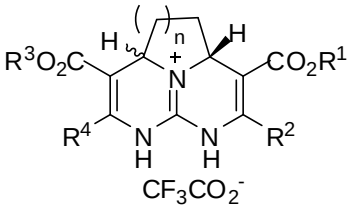
141 [77] X=OMe, NH_2

C4-C5 and C5-C6 Bonds



142 [56]

C2-N3 and N3-C4 Bonds



143 [56,66]

Figure 10. Chemical structures of bicyclic, tricyclic and tetracyclic dihydropyrimidines

VI. BIOLOGICAL ACTIVITIES

Investigations on the synthesis of dihydroheterocycles (dihydroazines) such as dihydropyridine,[79] dihydropyridazine,[80,81] dihydropyrimidine,[3,4] dihydropyrazine,[82-84] dihydropyran,[85] and dihydrothiopyran[73] were intensively carried out to find compounds with a variety of biological activities.[3i] For

instance, 3,4-dihydropyimidin-2(1*H*)-ones **1**[2a] synthesized by Biginelli exhibited antiviral,[74,86] antitumor,[87] antiinflammatory,[67,88] analgesic[88] activities, and properties of a platelet-activating factor (PAF) antagonist.[78] Khanina and coworkers discovered the cardiovascular activity of *N*-1-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones **1** in 1978.[89] Particularly, a lot of pharmaceutical companies all over the world studied the synthesis of dihydropyridines for the development of clinical candidates having cardiovascular activity. Dihydropyrimidines and dihydropyrazines[82-84] were regarded as aza-analogs of the dihydropyridines, such as nifedipine and nicardipine. Therefore, Cho's[3a,c,i] and Atwal's[4d-f] groups independently reported the synthesis of dihydropyrimidines **58** and **62** showing calcium antagonistic activity. Namely, Cho and coworkers found the regiospecific *N*-alkoxycarbonylation at the 3-position of Traube-Schwarz 1,4(1,6)-dihydropyimidine **57** (Scheme 8: eq. 29, 30) and successively achieved *N*-alkoxycarbonylation at the 3-position of Biginelli dihydropyimidine **61** (eq. 31).[3a,c,i] Although *N*-substituted 1,6-dihydropyrimidines **60** have an endocyclic π electron system in a dihydropyrimidine ring, *N*-substituted dihydropyrimidine-2(1*H*)-ones **62** have an exocyclic π electron system on a dihydro-pyrimidine ring. Therefore, they synthesized *N*-3-substituted dihydropyrimidine **62e** (R^1=CO_2Et, $CO_2C_7H_{15}$-*n*; R^2=*m*-$NO_2C_6H_4$; R^3=Et; R^4=H; Z=O) and *N*-1-substituted compound **62f** (R^1=H; R^2=*o*-$NO_2C_6H_4$; R^3=Et; R^4=$CO_2C_7H_{15}$-*n*; Z=O). After detailed studies on the structure-activity relationship of a series of compounds **58**, **60**, and **62**, the compound **144** exhibited not only more potent and longer lasting vasodilative action but also a more hypotensive activity with a slow onset than dihydropyridines (nifedipine and nicardipine).[3i] Moreover, **144** was less effective in blocking atrioventricular conduction in dogs and less toxic than dihydropyridines (nicardipine and nilvadipine). On the other hand, the *N*-3 substituted dihydropyrimidine **62e** showed a more potent and longer lasting vasodilative activity but the *N*-1-substituted compound **62f** did not show any activity.

On the other hand, Atwal and coworkers synthesized a series of *N*-3 substituted dihydropyrimidines **62**.[4d-g] After extensive studies of the structure-activity relationship, they finally found one of the most

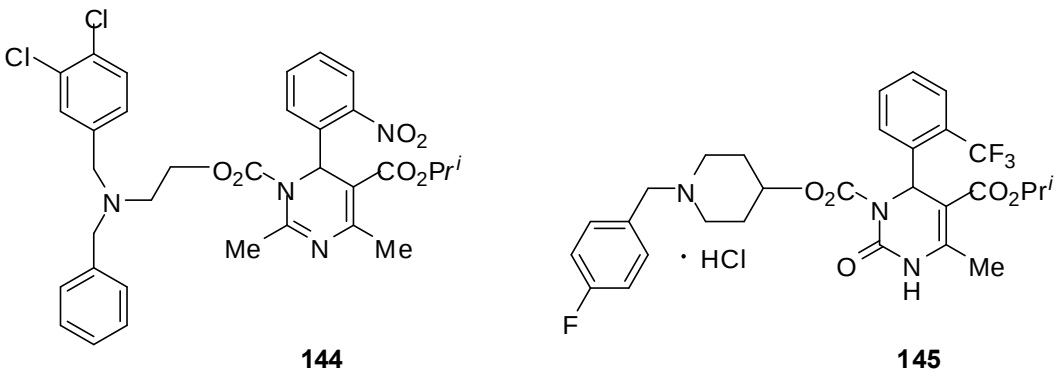
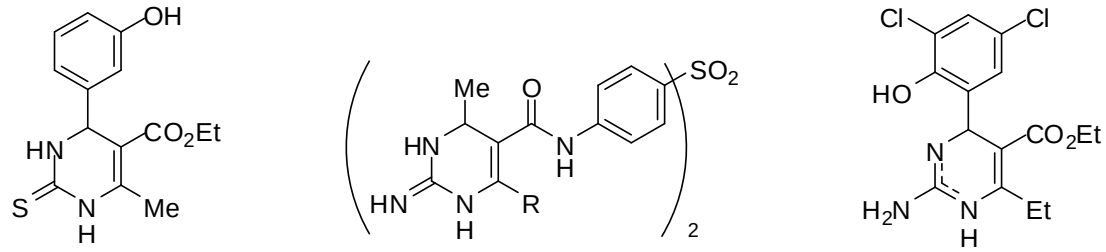


Figure 11. Representative dihydropyrimidines as potent calcium antagonists

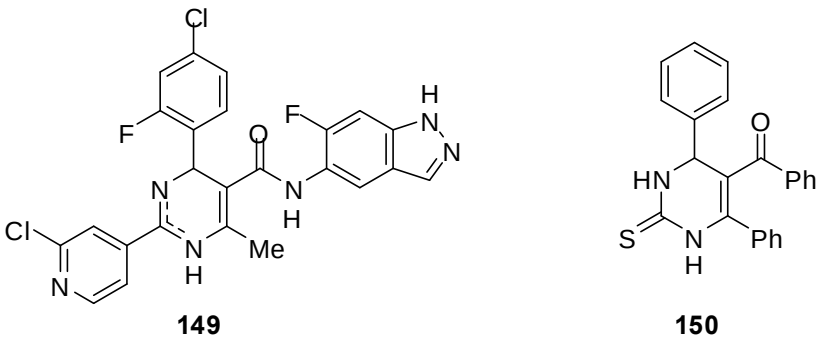
potent compounds, dihydropyrimidin-2-one **145** [(*R*)-enantiomer],[4f] which has comparable pharmacological profiles to amlodipine.

Recently, 3,4-dihydropyrimidine-2(1*H*)-thione **146** (monastrol)[90, 91] has been reported as a kinesin spindle protein inhibitor.[92] Monastrol arrests mammalian cells in mitosis with monopolar spindles. In vitro, it specifically inhibits the motility of the mitotic kinesin Eg5, a motor protein required for spindle bipolarity.[93] Therefore, monastrol is a particularly useful tool for studying mitotic mechanisms.[92] A series of bis dihydropyrimidine compounds **147a-f** (R=C_6H_5, 4-FC_6H_4, 2-ClC_6H_4, 2,6-diClC_6H_3, 4-$NO_2C_6H_4$, furyl) were synthesized and evaluated for their antimycobacterial activity.[93] Among them, **147b** (R=4-FC_6H_4) exhibited the most potent activity against *M. tuberculosis* H_{37} Rv and INH resistant *M. tuberculosis* with minimum inhibitory concentrations (MICs) of 0.08 and 0.10 μM, respectively. Emmacin **148**, an anti-MRSA agent discovered from a diversity-oriented synthesis, represents a new structural subclass of bacterial dihydrofolate reductase inhibitors.[94] Moreover, potent, selective and orally bioavailable dihydropyrimidine inhibitors **149** of Rho kinase (ROCK1) as potential therapeutic agents for cardiovascular diseases have recently been reported.[95]

In materials science fields, the inhibition and adsorption effects of 5-benzoyl-4-(substituted phenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thiones (and -ones) on the corrosion behavior of austenitic stainless steel in 0.5M H_2SO_4 were studied by electrochemical methods. Among them, **150** was found to be a good anticorrosion agent for stainless steel.[17]



146 monastrol **147** **148 emmacin**



149 **150**

Figure 12. Dihydropyrimidines exhibiting a variety of biological activities

VII. CONCLUSION

In this review, the synthesis history, physical properties (stability and tautomerism), ring construction procedures for dihydropyrimidine skeletons, various reactions from dihydropyrimidines, and biological activities of monocyclic dihydropyrimidines are described in detail. The modification of substituents on the dihyropyrimidine skeleton should be further performed in future research, as well as efforts to stabilize such a skeleton. However, despite the many biological active compounds synthesized, no compounds have found practical use so far. In future research, more useful compounds may be produced from both academic and practical viewpoints. In addition, the synthesis of bicyclo-, spiro-, bicyclic, tricyclic, and tetracyclic dihydropyrimidines should be further studied, despite the many examples that have already been reported for multicyclic dihydropyrimidines. Novel bicyclic and tricyclic dihydropyrimidines may exhibit interesting biological activities and may be more stable than monocyclic dihydropyrimidines, although their bioavailability, metabolism, and toxicology must still be carefully investigated.

This review might be useful for the future synthesis of monocyclic and multicyclic dihydropyrimidines which could be promising compounds from the biological and pharmaceutical viewpoints.

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