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# SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES USING CONJUGATE ADDITION REACTIONS OF NUCLEOPHILES TO $\alpha,\beta$-UNSATURATED IMINES

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**Abstract** – Synthetic methods for the synthesis of nitrogen-containing heterocycles are of utmost interest and importance because these structures are the key components of natural and unnatural biologically active compounds and functionalized materials. This review summarizes the synthesis of nitrogen-containing heterocycles, where the conjugate addition of nucleophiles to $\alpha,\beta$-unsaturated imines is the crucial step.

## CONTENTS

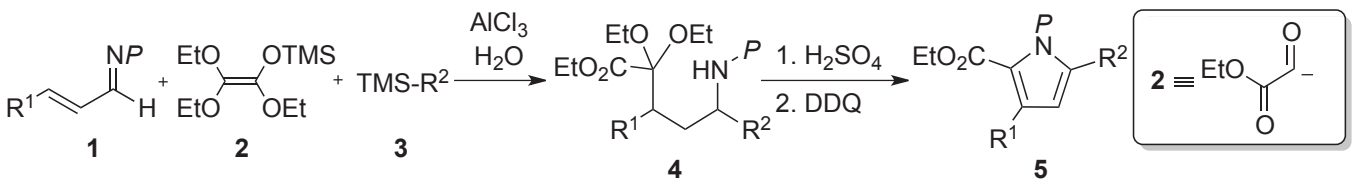
## 1. INTRODUCTION

The development of new, efficient synthetic methods for the synthesis of nitrogen-containing heterocycles is extensively studied, because many nitrogen-containing heterocycles, such as nucleic acid bases, vitamins, amino acids, alkaloids, and $\beta$-lactams, exhibit biological activities and are useful as functionalized materials for organic electronics or photonics. Imines, one of the most useful types of nitrogen-containing compounds, are typically prepared by the condensation of carbonyl compounds with primary amines via dehydration. This review describes new synthetic methods for the synthesis of nitrogen-containing heterocycles via the conjugate addition reactions of nucleophiles to $\alpha,\beta$-unsaturated imines.

## 2. SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES VIA 1,4- AND 1,2-DOUBLE NUCLEOPHILIC ADDITION REACTIONS

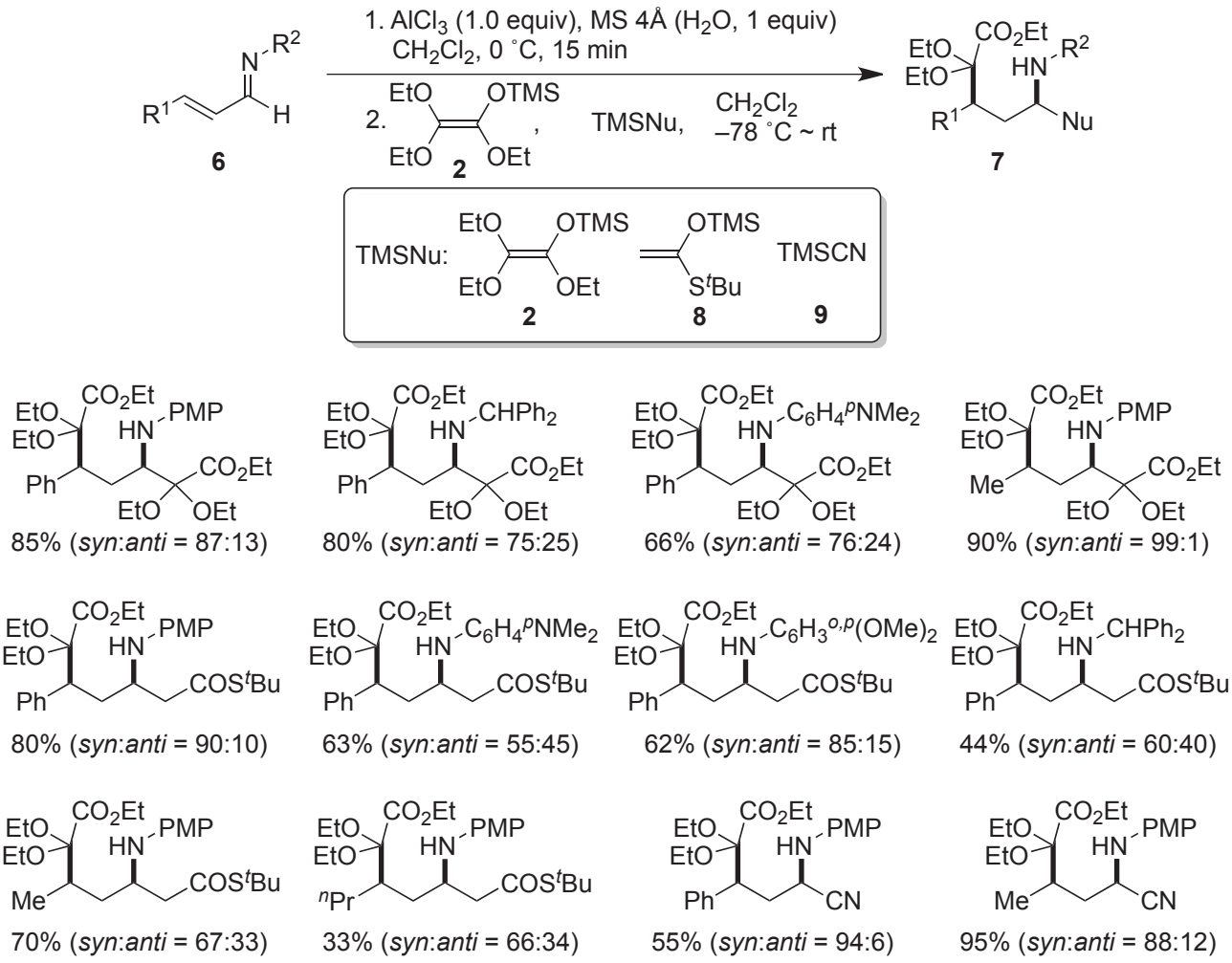
### 2-1. Synthesis of 2,3,5-trisubstituted pyrroles

Pyrrole derivatives have widespread biological importance,[1] and therefore, it is increasingly important to construct such skeletons in an efficient manner.[2] A potentially effective approach for the construction of the pyrrole ring involves cyclization of $\gamma$-amino carbonyl compounds followed by dehydrogenation. For the synthesis of γ-amino carbonyl compounds, crucial intermediates in this strategy, the nucleophilic addition to $\gamma$-oxoimines constitutes a straightforward pathway. However, difficulty has been encountered frequently in the synthesis of $\gamma$-oxoimines due to their susceptibility to hydrolysis and/or isomerization.[3] For the circumvention of such a drawback of isolating these relatively unstable imine intermediates as well as to use an operationally simple experimental procedure, we introduced a double nucleophilic addition reaction to $\alpha,\beta$-unsaturated imines **1**.[4] When $\alpha,\alpha$-dialkoxy ketene silyl acetal **2**, an acyl anion equivalent, is used as the first nucleophile, this methodology offers a facile synthetic route to $\gamma$-amino carbonyl synthons **4**, which on treatment with sulfuric acid followed by oxidation with DDQ gave 2,3,5-trisubstituted pyrroles **5** in good yields.[5]



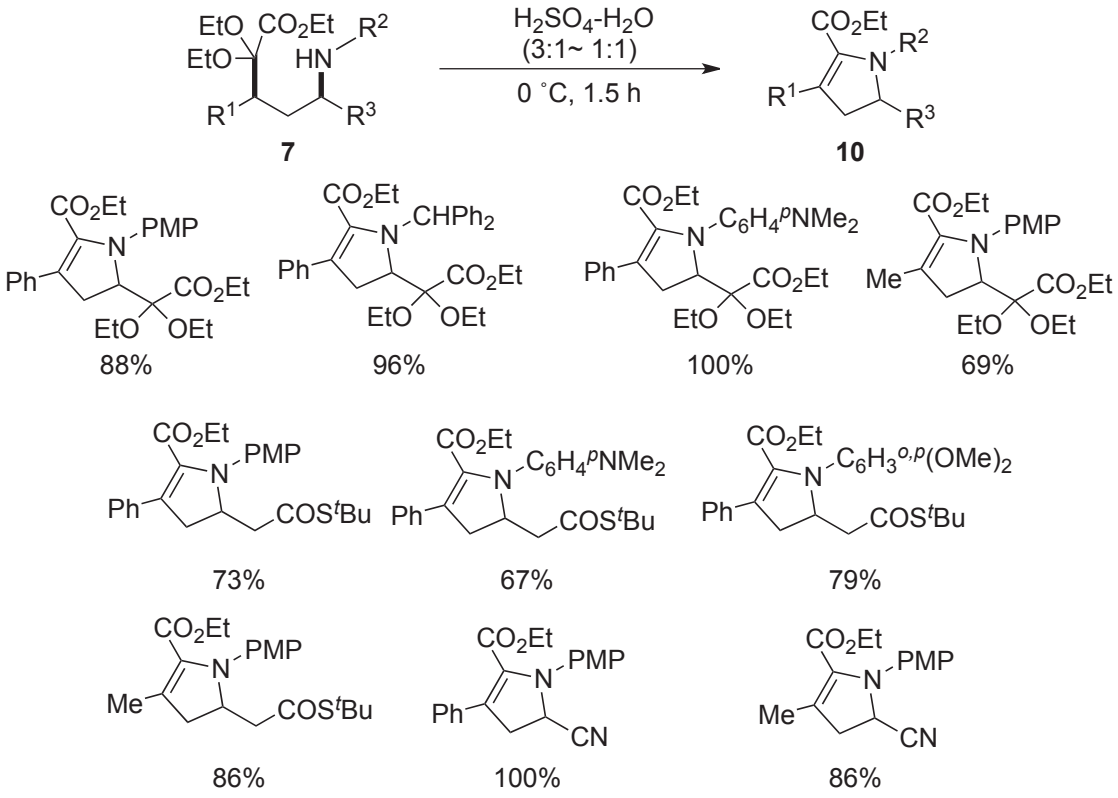

**Scheme 1.** 2,3,5-Trisubstituted Pyrrole Synthesis

The following examples show the double nucleophilic addition (Scheme 2), cyclization (Scheme 3), and dehydration (Scheme 4).

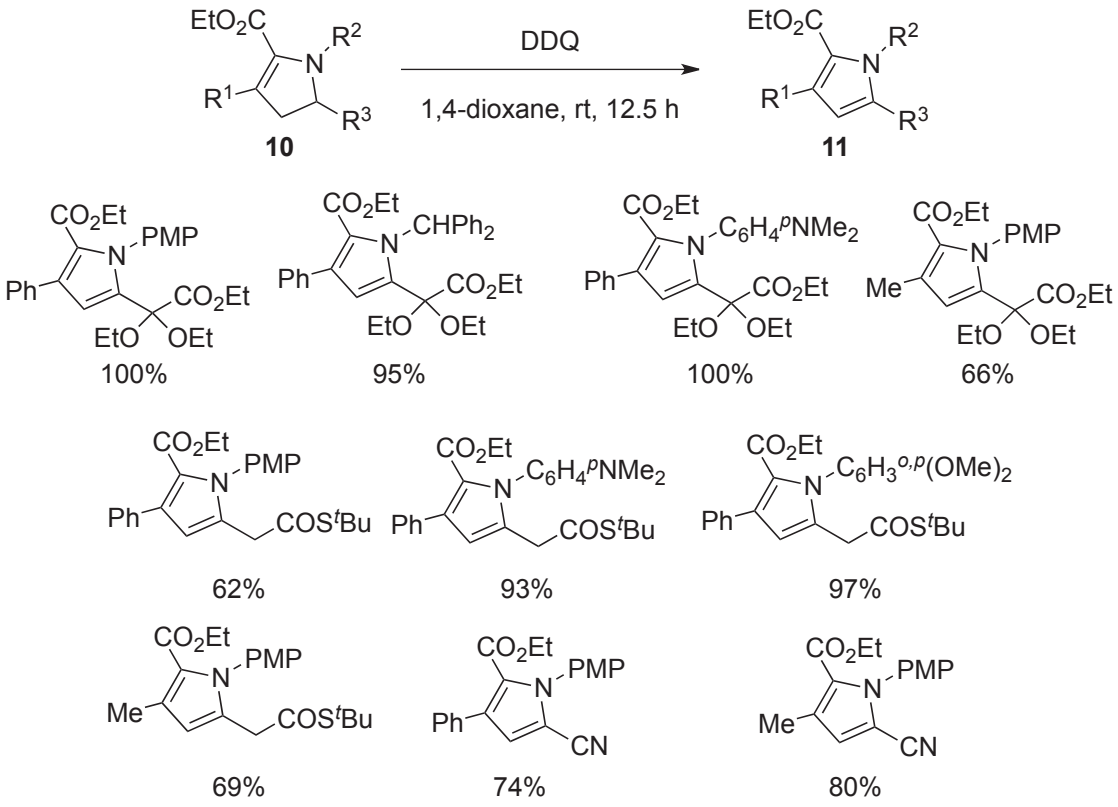



**Scheme 2.** Double Nucleophilic Addition

To synthesize *γ*-amino carbonyl compounds, this reaction was carried out using imine **6** and ketene silyl acetal **2** in $CH_2Cl_2$ in the presence of aluminum chloride and MS 4 Å containing $H_2O$ from –78 °C to room temperature to give the double addition product **7** in good yield with *syn*-selectivity. In addition, the use of ketene silyl thioacetal **8** or trimethylsilyl cyanide (**9**) as the second nucleophile with ketene silyl acetal **2** as the first nucleophile gave the double addition products **7** in good yields. The ketene silyl acetal **2** underwent 1,4-addition, while the ketene silyl thioacetal **8** or trimethylsilyl cyanide (**9**) underwent 1,2-addition in a highly regioselective manner. All of the 1,4- and 1,2-addition products **7** were readily converted into the corresponding multi-substituted pyrroles **11** via cyclization into the dihydropyrrole **10** with $H_2SO_4$ followed by dehydrogenation with DDQ. Both steps proceeded well to give these products in good to high yields.

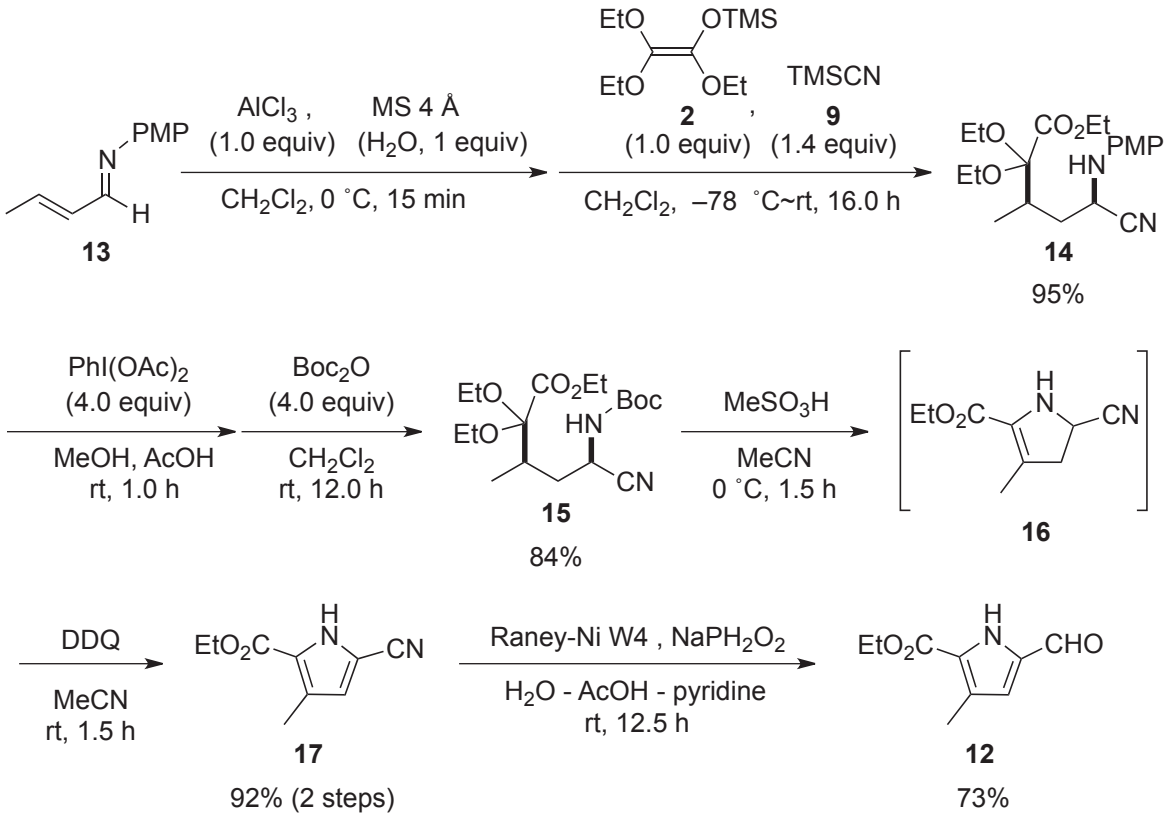



**Scheme 3.** Cyclization




**Scheme 4.** Dehydration

This transformation into 2,3,5-trisubstituted pyrroles enabled a six-step synthesis of imidazole glycerol phosphate dehydratase inhibitors (IGPDIs), which exhibit herbicidal activity.[6] The synthesis of the IGPDI **12** was carried out in the following manner (Scheme 5). The ketene silyl acetal **2** and trimethylsilyl cyanide (**9**) were treated with *N*-4-methoxycrotylideneamine **13** in the presence of $AlCl_3$ to give the doubly alkylated product **14** in 95% yield. Switching of the PMP group for a Boc analogue was carried out before cyclization into the pyrrole. The Boc-protected double-addition product **15** was treated with $MeSO_3H$ and DDQ to afford the pyrrole **17** in 92% yield (2 steps), where the NH-free dihydropyrrole intermediate **16** was not isolated. Finally, reduction of the cyano group with Raney-Ni W4 in the presence of $NaPH_2O_2$ gave the desired monopyrrole aldehyde **12** in 73% yield.



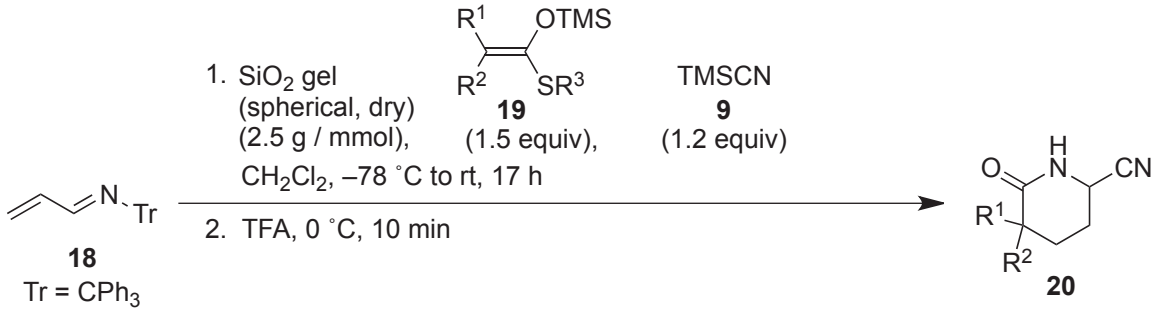

**Scheme 5.** Synthesis of the IGPDI **12**

## 2-2. Synthesis of *δ*-Lactams

*δ*-Lactams are frequently observed in natural products, such as strychnine, matrine, and surugatoxin, and their derivatives are useful for the preparation of drug-like molecules. They are important synthetic building blocks for the development of medicinally active compounds, and many of them are of great interest because of their unique biological activities.[7] As mentioned above, we introduced a double nucleophilic addition reaction to *α*,*β*-unsaturated imines using several nucleophiles.[4,5,8] For the reaction with *N*-allylideneamine **18**, when the trisubstituted ketene silyl thioacetal **19** derived from *S*-cyclohexyl

propanethioate was used in the presence of dried silica gel, the cyclized *δ*-lactam **20** was obtained in high yield by workup with trifluoroacetic acid (TFA) (Table 1, entry 1).[9] The trisubstituted ketene silyl thioacetals **19** gave the corresponding *δ*-lactams **20** in moderate to good yields (entries 1–6). The use of a tetrasubstituted analogue also gave the product **20** in moderate yield (entry 7).

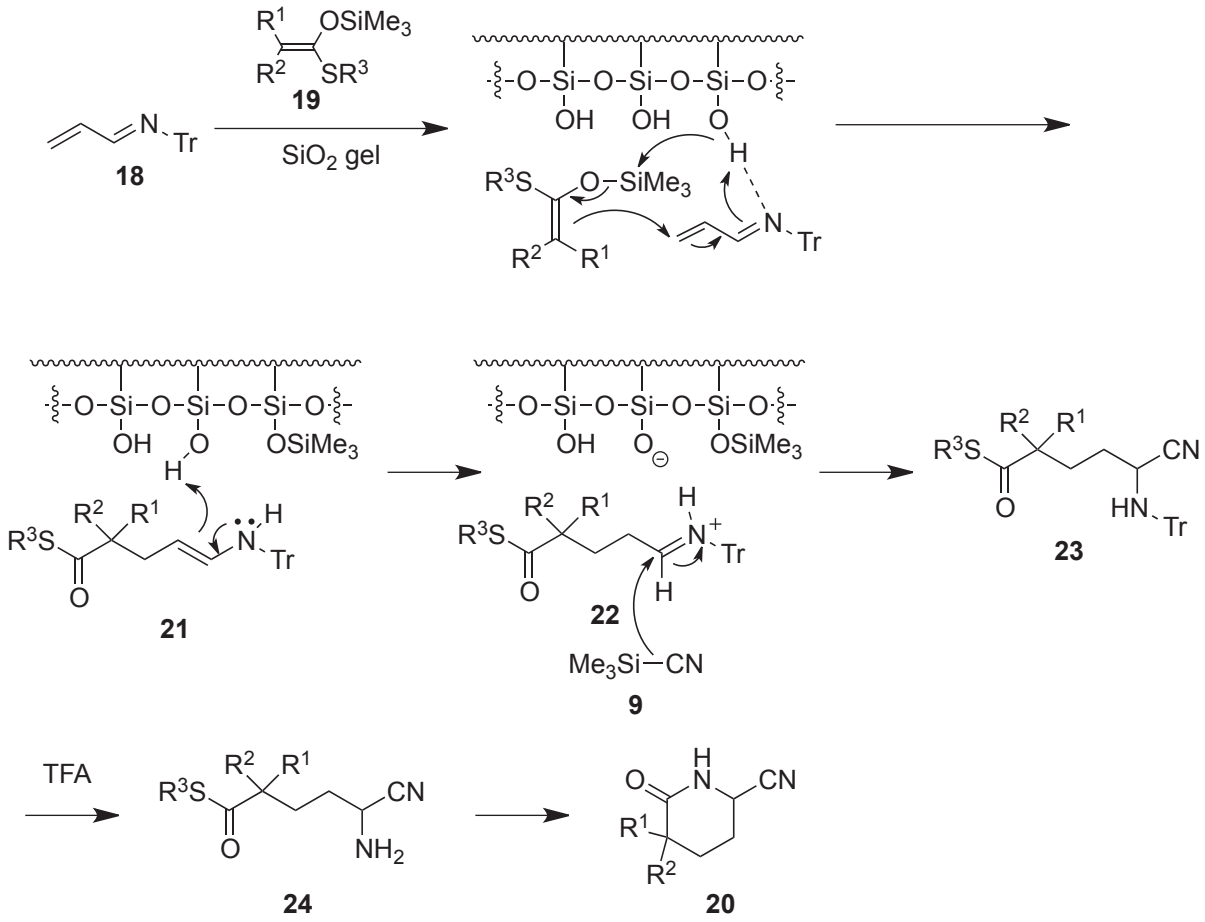
**Table 1.** Synthesis of *δ*-Lactams **20** Using Double Nucleophilic Addition of *N*-Allylideneamine **18** with Ketene Silyl Thioacetals **19**




| Entry | $R^1$ OTMS / $R^2$ $SR^3$ | Yield (%) | dr | Entry | $R^1$ OTMS / $R^2$ $SR^3$ | Yield (%) | dr |
|---|---|---|---|---|---|---|---|
| 1 | OTMS, $S^cHex$ (*Z*/*E* = 92/8) | 85 | 53/47 | 5 | OTMS, SPh (*Z*/*E* = 73/23) | 64 | 42/58 |
| 2 | OTMS, SEt (*Z*/*E* = 91/9) | 76 | 50/50 | 6 | OTMS, $S^nPr$ (*Z*/*E* = 88/12) | 40 | 46/54 |
| 3 | OTMS, $S^tBu$ (*Z*/*E* = 94/6) | 71 | 47/53 | 7 | OTMS, SEt | 53 | — |
| 4 | OTMS, $S^iPr$ (*Z*/*E* = 92/8) | 35 | 66/34 | | | | |

[a] Treatment with TFA at room temperature for 10 min. [b] The reaction time was 24 h.

A proposed reaction mechanism is shown in Scheme 6. First, the *N*-allylideneamine **18** is activated with silica gel followed by 1,4-addition of ketene silyl thioacetal **19** to give an intermediary enamine species **21**. Isomerization to iminium species **22** is then promoted by silica gel followed by the 1,2-addition of TMSCN **9** to give the 1,4- and 1,2-products **23**. Deprotection of the trityl group with TFA gives amino nitrile **24**, which cyclizes into *δ*-lactams **20**.



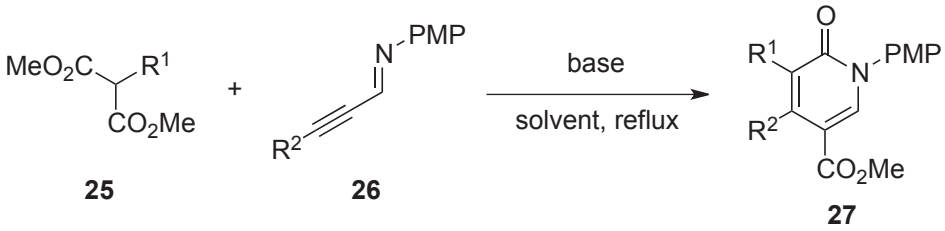
**Scheme 6.** Possible Reaction Mechanism for the Synthesis of *δ*-Lactams **20**

## 3. SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES VIA CONJUGATE ADDITION OF NUCLEOPHILES TO ALKYNYL IMINES

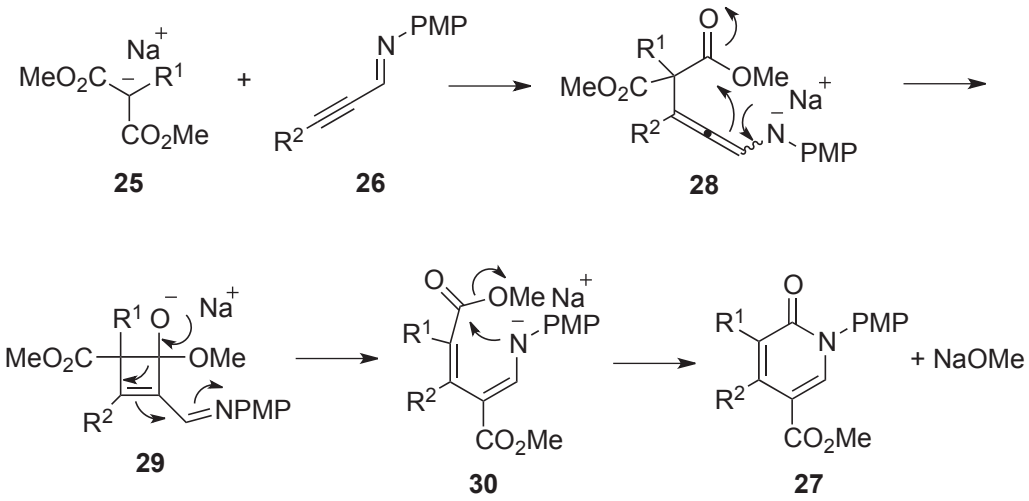
### 3-1. Synthesis of Multi-substituted 2-Pyridones

Alkynyl imines are one of the most important nitrogen-containing starting materials because of their extensive use in the synthesis of heterocycles including nitrogen atoms, such as pyrazoles,[10] pyrimidines,[10] pyrrolinones,[11] pyrroles,[2g] indolizines,[2g] quinolines,[12] fused pyrrolines,[12] and pyridines.[13] In addition, alkynyl imines are used in [2+2]-cycloaddition reactions with ketenes or the reaction with several enolates to give *β*-lactams.[14] The reactivity at the *β*-position of alkynyl imines is of particular interest. For example, the reaction of the sodium salt of dimethyl alkylmalonate **25** with alkynyl imine **26** proceeds in moderate to high yields to give the 2-pyridone **27** bearing a 5-methoxycarbonyl group.[15] The development of synthetic methods for the preparation of functionalized 2-pyridone is important because a large number of biologically active compounds contain the 2-pyridone structure.[16] Representative examples of this 2-pyridone synthesis are summarized in Table 2.

**Table 2.** Synthesis of Multi-substituted 2-Pyridones **27** via Conjugate Addition of Malonic Esters **25** to Alkynyl Imines **26**




| Entry | $R^1$ | $R^2$ | Base | Solvent | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Me | Ph | NaOMe | 1,4-dioxane | 2 | 91 |
| 2 | Me | Bu | NaH | 1,4-dioxane | 2 | 71 |
| 3 | Me | $TBSO(CH_2)_3$ | NaH | 1,4-dioxane | 2 | 57 |
| 4 | Me | 1-cyclohexenyl | NaH | 1,4-dioxane | 12 | 82 |
| 5 | allyl | Ph | NaH | THF | 23 | 59 |
| 6 | allyl | $TBSO(CH_2)_3$ | NaH | THF | 20 | 46 |
| 7 | allyl | 1-cyclohexenyl | NaH | 1,4-dioxane | 8 | 63 |



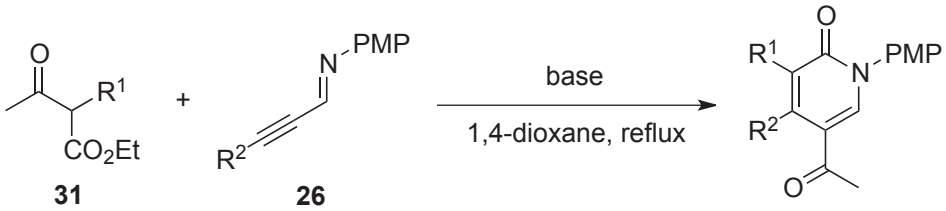

**Scheme 7.** Possible Reaction Mechanism for the Synthesis of 2-Pyridone **27**

Both aromatic and aliphatic imines can be used to produce the 2-pyridones **27** in moderate to good yields. Even when the steric bulk of the nucleophile was increased, as with dimethyl allylmalonate **25** ($R^1$ = allyl), the 2-pyridones **27** were obtained in moderate yields (entries 5–7). Although numerous methods for the synthesis of 2-pyridones have been reported,[17] the present 2-pyridone synthesis is an attractive alternative because alkynyl imines and substituted malonic esters are readily available.

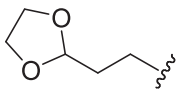
A possible reaction mechanism is shown in Scheme 7. The metalloallenamine **28** would be generated via a 1,4-addition reaction of the sodium salt of dimethyl methylmalonate **25** to alkynyl imine **26** and undergo an intramolecular cyclization to give cyclobutenoxide **29**. The cyclobutenoxide **29** would collapse into the metalloenamine **30** via a ring-opening reaction to release the ring strain of the cyclobutene, followed by subsequent cyclization to give the 2-pyridone **27**.

When *β*-keto esters **31** were used as the nucleophile instead of 2-substituted malonic esters **25**, the reactions with imines **26** gave 5-acetyl-2-pyridones **32** in moderate yields (Table 3).[18]

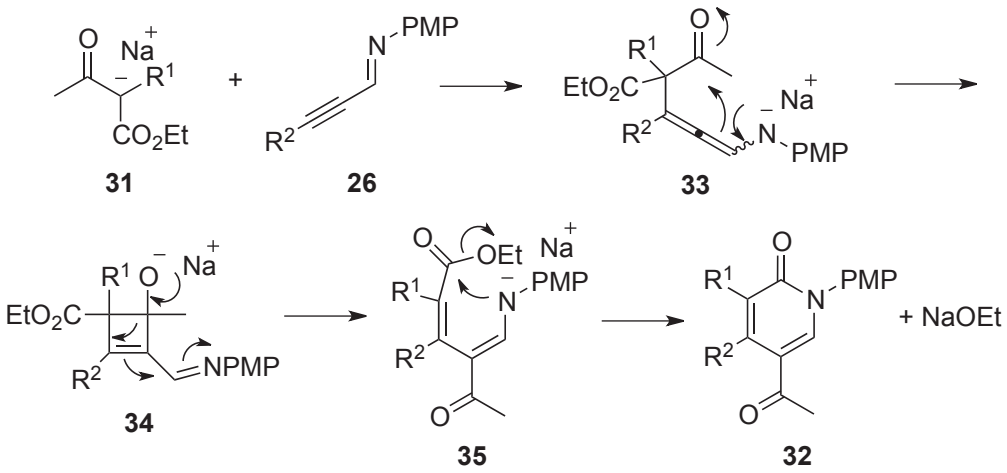
**Table 3.** Synthesis of 5-Acetyl-2-pyridones **32** via Conjugate Addition of *β*-Keto Esters **31** to Alkynyl Imines **26**




**31** **26** **32**

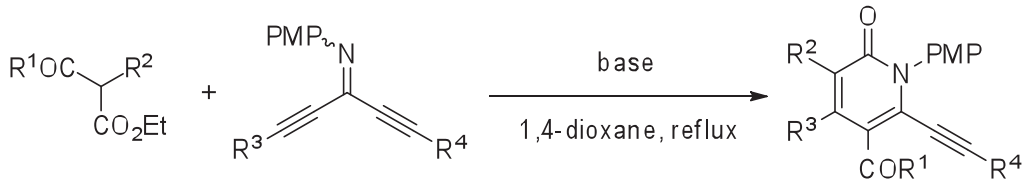
| Entry | $R^1$ | $R^2$ | Base | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Me | Ph | NaOEt | 21 | 64 |
| 2 | Me | Bu | NaH | 20 | 58 |
| 3 | Me | $TBSO(CH_2)_3$ | NaH | 21 | 69 |
| 4 | Me | 1-cyclohexenyl | NaH | 21 | 31 |
| 5 | allyl | Ph | NaOEt | 21 | 49 |
| 6 | allyl | Bu | NaH | 18 | 47 |
| 7 | allyl | $TBSO(CH_2)_3$ | NaH | 21 | 33 |
| 8 |  | Ph | NaOEt | 15 | 45 |

A possible reaction mechanism is shown in Scheme 8. The metalloallenamine **33** generated via the 1,4-addition reaction of the sodium salt of *β*-keto ester **31** to alkynyl imine **26** undergoes an intramolecular cyclization at the more reactive keto carbonyl group to give the cyclobutenoxide **34**. The cyclobutenoxide **34** is then transformed into the metalloenamine **35** via ring-opening, and subsequent cyclization gives the 5-acetyl-2-pyridone **32**.

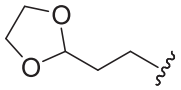



**Scheme 8.** Possible Reaction Mechanism for the Synthesis of 5-Acetyl-2-pyridone **32**

**Table 4.** Synthesis of 3,4,5,6-Tetrasubstituted 2-Pyridones **38** via Conjugate Addition of Active Methine Compounds **36** to Dialkynyl Imines **37**




**36** **37** **38**

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Base | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | OEt | Me | Ph | Ph | NaOEt | 6 | 66 |
| 2 | OEt | Me | Bu | Bu | NaOEt | 9 | 44 |
| 3 | Me | Me | Ph | Ph | NaOEt | 14 | 52 |
| 4 | Me | Me | Bu | Bu | NaH | 14 | 56 |
| 5 | OEt | Me | Ph | TBS | NaH | 1 | 71 |
| 6 | OEt | allyl | Bu | TBS | NaH | 21 | 55[a] |
| 7 | Me | Me | Ph | TBS | NaOEt | 7 | 40 |
| 8 | Me | Me | Bu | TBS | NaOEt | 12 | 51 |
| 9 | Me | allyl | Bu | TBS | NaH | 21 | 42 (12)[b] |
| 10 | OEt |  | H | TBS | NaOEt | 5.5 | 51 |

[a] 2-Pyridone **38** ($R^2$ = (*E*)-1-propenyl) possessing a double bond that isomerized internally was obtained.

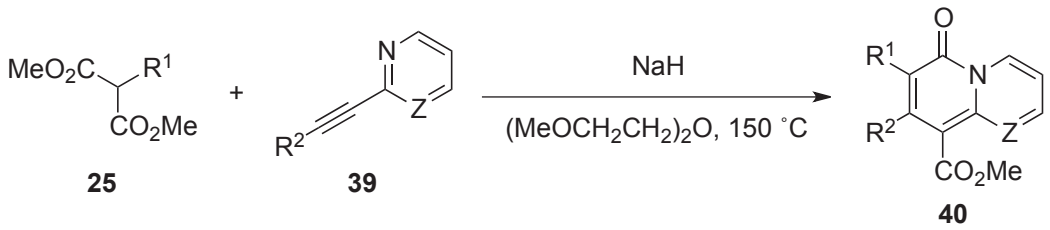
[b] Yield of 2-pyridone **38** ($R^2$ = (*E*)-1-propenyl) possessing a double bond that isomerized internally.

The synthesis of 3,4,5,6-tetrasubstituted 2-pyridone was carried out via the nucleophilic addition of active methine compounds to dialkynyl imines with the goal of achieving the synthesis of (-)-A58365A. This compound was obtained in the Eli Lilly laboratories from a fermentation broth of the bacterium Streptomyces chromofucus and found to be an angiotensin-converting enzyme inhibitor at nanomolar concentrations.[19,20] The reaction of active methine compounds **36**, such as malonic esters or β-keto esters, to dialkynyl imines **37** proceeded to give 3,4,5,6-tetrasubstituted-2-pyridones **38** in moderate to good yields (Table 4).[21] The reaction of unsymmetrical dialkynyl imine **37** proceeded regioselectively to give only 2-pyridone **38**, where the less hindered sp carbon reacted preferentially (entries 5–10).

### 3-2. Synthesis of Multi-substituted Bicyclo-2-pyridones[22]

Bicyclic compounds containing a 2-pyridone structure are key intermediates for the total synthesis of anagyrine,[23] lupinine,[23a] and ipalbidine.[24] In addition, there are biologically active compounds possessing a 2-pyridone structure, such as (-)-A58365A.[19,20] 2-Alkynylpyridine **39** (Z = CH) and 2-alkynylpyrimidine **39** (R = N) were used as a cyclic alkynyl imine equivalent. The reaction of 2-alkynylpyridines **39** (Z = CH) or 2-phenylethynylpyrimidine **39** (Z = N) with several malonic esters **25** proceeded to give *4H*-quinolizin-4-ones **40** (Z = CH) or *6H*-pyrido[1,2-*a*]pyrimidin-6-ones **40** (Z = N), respectively, in moderate to good yields (Table 5).

**Table 5.** Synthesis of *4H*-Quinolizin-4-ones **40** (Z = CH) and *6H*-Pyrido[1,2-*a*]pyrimidin-6-ones **40** (Z = N)



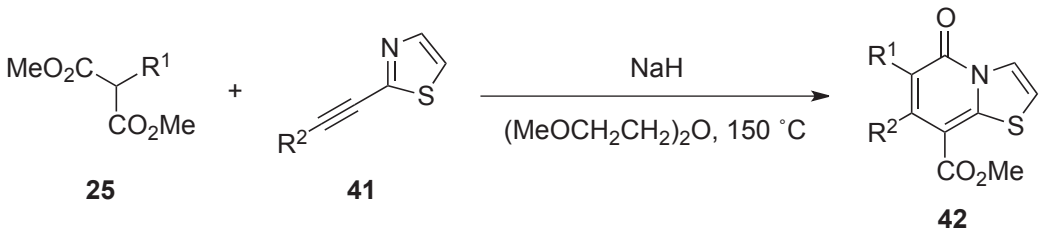

**25** **39** **40**

| Entry | $R^1$ | $R^2$ | Z | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Me | Ph | CH | 22 | 38 |
| 2 | Me | Bu | CH | 23 | 36 |
| 3 | Me | $Me_3Si$ | CH | 12 | 56[a] |
| 4 | 4-$MeOC_6H_4$ | H | CH | 8 | 77 |
| 5 | 2-pyridyl | H | CH | 8 | 43 |
| 6 | Me | Ph | N | 22 | 48 |
| 7 | allyl | Ph | N | 22 | 30 |

[a] Desilylated product **40** ($R^2$ = H) was obtained.

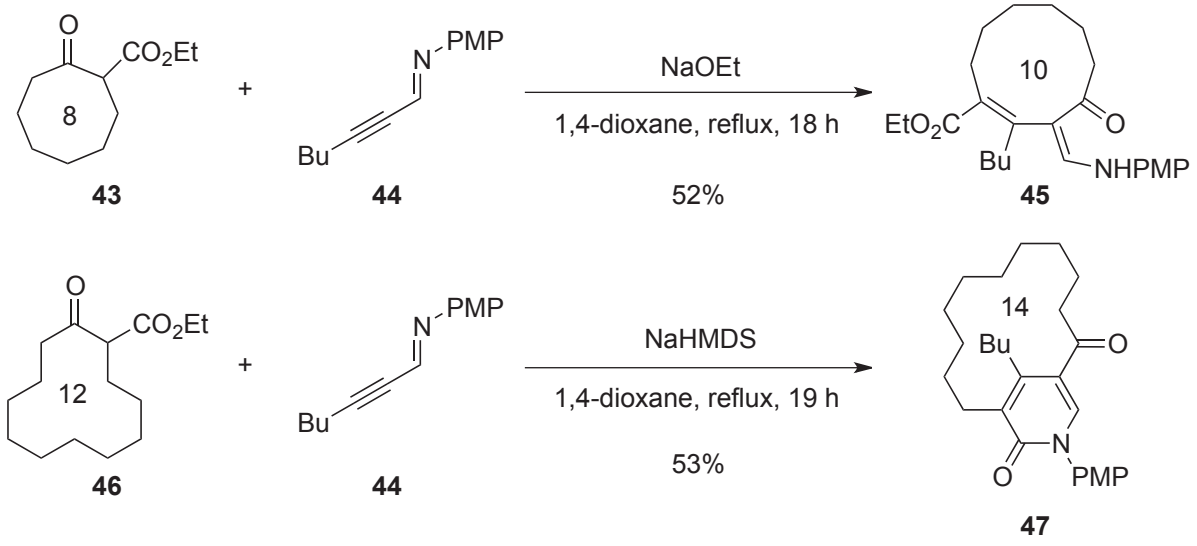
The use of 2-alkynylthiazoles **41** as a cyclic alkynyl imine equivalent gave *5H*-thiazolo[3,2-*a*]pyridin-5-ones **42** in good to high yields (Table 6).

**Table 6.** Synthesis of 5*H*-Thiazolo[3,2-*a*]pyridin-5-ones **42**



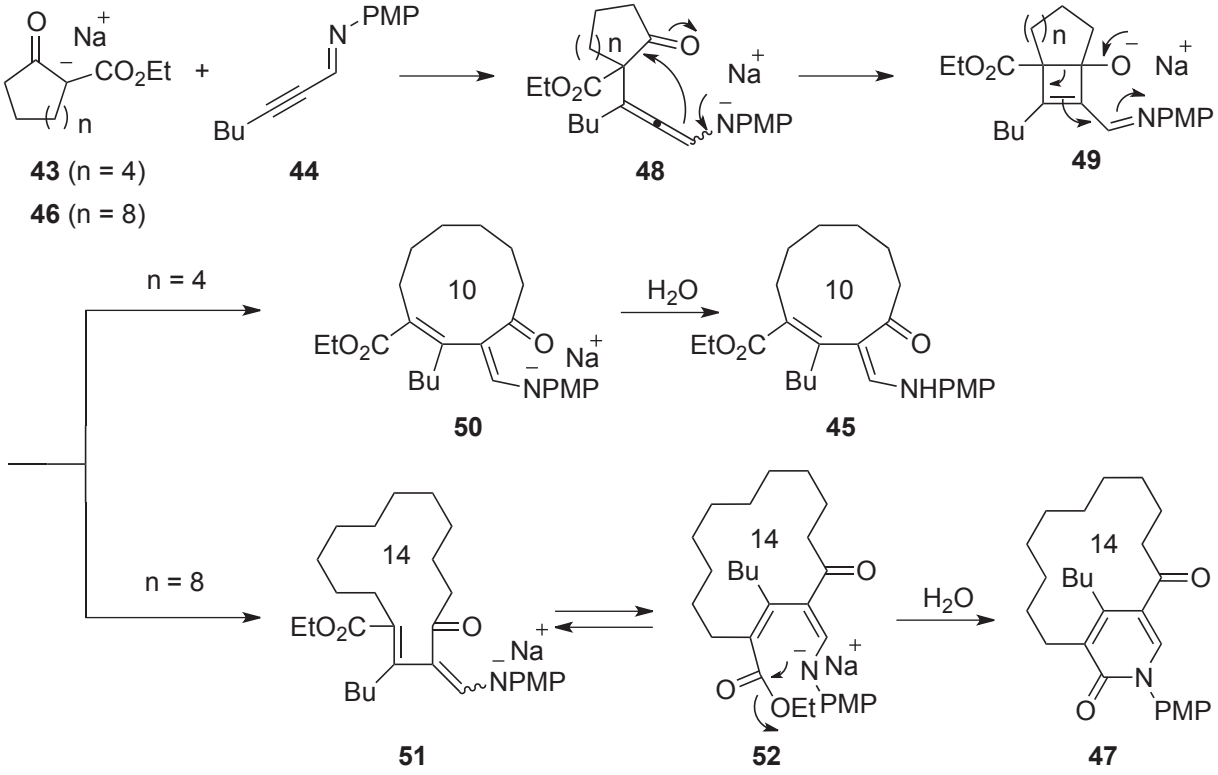

| Entry | $R^1$ | $R^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | Me | Ph | 22 | 83 |
| 2 | allyl | Ph | 20 | 61 |
| 3 | Me | Bu | 8 | 75 |
| 4 | allyl | Bu | 18 | 53 |

When cyclic *β*-keto ester **43** was used in the conjugate addition reactions with alkynyl imine **44** instead of the acyclic derivatives, the ring expansion reactions proceeded via cyclobutenoxide as a Grob-type fragmentation intermediate to give the two-atom enlarged carbocyclic product **45** possessing a masked formyl group.[25] During the investigation of the ring expansion reaction, when the ethyl 2-oxocyclododecanecarboxylate (**46**), a more flexible molecule, was used as the *β*-keto ester, the reaction with alkynyl imine **44** gave the bicylo-2-pyridone **47** in 53% yield (Scheme 9).




**Scheme 9.** Synthesis of the Two-atom Enlarged Carbocycle **45** and Bicyclo-2-pyridone **47**

A plausible reaction mechanism is shown in Scheme 10. Metalloallenamine **48** would be generated via a conjugate addition of the sodium salt of *β*-keto esters **43** or **46** to alkynyl imine **44**, and undergo a chemoselective intramolecular cyclization at the keto carbonyl group to give the cyclobutenoxide intermediate **49**. The cyclobutenoxide **49** (n = 4) would collapse into the metalloenamine **50** via a ring-opening reaction to release the ring strain in the cyclobutene, and subsequent protonation with water to quench the reaction would give the ring expansion product **45**. On the other hand, in the reaction of ethyl 2-oxocyclododecanecarboxylate (**46**), (*E*)-metalloenamine **51** generated via the ring-opening reaction would isomerize into (*Z*)-metalloenamine **52** because of the flexibility of the large carbocycle, and subsequent cyclization would give bicylo-2-pyridone **47**.



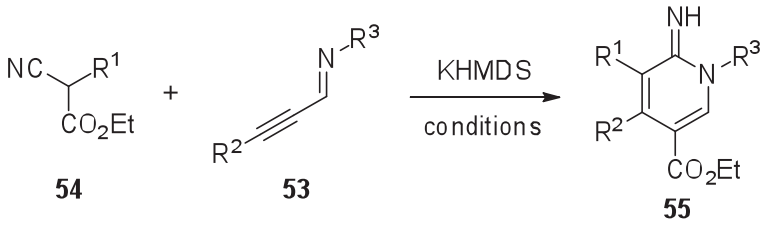

**Scheme 10.** Plausible Reaction Mechanism for the Ring-expansion Reaction

### 3-3. Synthesis of Multi-substituted 2-Iminopyridines and 2-Aminopyridines[26]

Biologically active compounds containing a 2-iminopyridine structure are less known than those containing the 2-pyridone counterpart;[27] however, 2-iminopyridines are highly attractive compounds compared with members of the large group of biologically active 2-pyridones.[16,28] Several methods for the synthesis of 2-iminopyridines via the condensation of cyano derivatives[29] and other reactions[30] using transition metals have been reported. However, the former methods are not yet satisfactory from the viewpoint of synthesizing 2-iminopyridines possessing the desired substituents. Therefore, the

development of alternative synthetic methods is requied for the preparation of multi-substituted 2-iminopyridines from readily available starting materials. On the basis of our 2-pyridone synthesis, the reaction of alkynyl imines **53** was carried out with ethyl cyanoacetate derivatives **54**. The reaction of alkynyl imines **53** bearing *p*-methoxyphenylmethyl (MPM) and *p*-methoxyphenyl (PMP) groups at the nitrogen proceeded with ethyl cyanoacetate derivatives **54** to give the corresponding 2-iminopyridines **55** ($R^3$ = MPM or PMP) in moderate to good yields (Table 7).

**Table 7.** Synthesis of Multi-substituted 2-Iminopyridines **55**



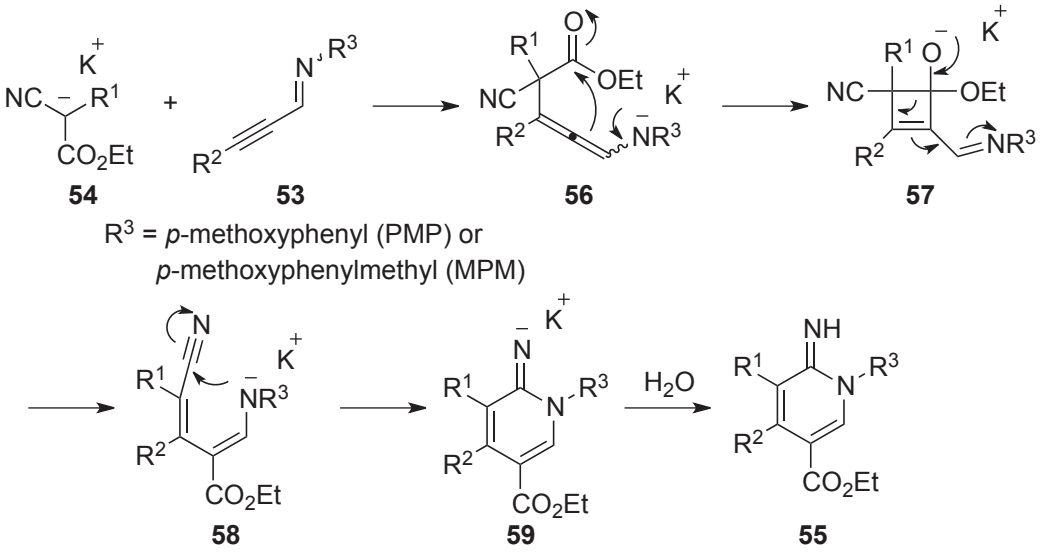

**54** **53** **55**

| Entry | $R^1$ | $R^2$ | $R^3$ | Conditions[a] | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Me | Ph | MPM | A | 20 | 70 |
| 2 | Me | 1-cyclohexenyl | MPM | A | 3.5 | 57 |
| 3 | Me | Bu | MPM | A | 3.5 | 47 |
| 4 | Me | Ph | MPM | B | 45 | 51 |
| 5 | Ph | Ph | PMP | C | 25 | 81 |
| 6 | Me | 1-cyclohexenyl | PMP | C | 19 | 84 |
| 7 | Me | Bu | PMP | C | 20 | 48 |
| 8 | Me | Ph | PMP | B | 21.5 | 84 |
| 9 | Ph | 1-cyclohexenyl | PMP | B | 20 | 45 |
| 10 | Ph | Bu | PMP | B | 20 | 50 |
| 11 | allyl | Ph | PMP | B | 16 | 66 |
| 12 | allyl | 1-cyclohexenyl | PMP | B | 16 | 66 |

[a] Conditions A: in $(MeOCH_2CH_2)_2O$/toluene (3.1:1) at 160 °C. Conditions B: in 1,4-dioxane under reflux. Conditions C: in 1,4-dioxane/toluene (2.4-3.1:1) under reflux.

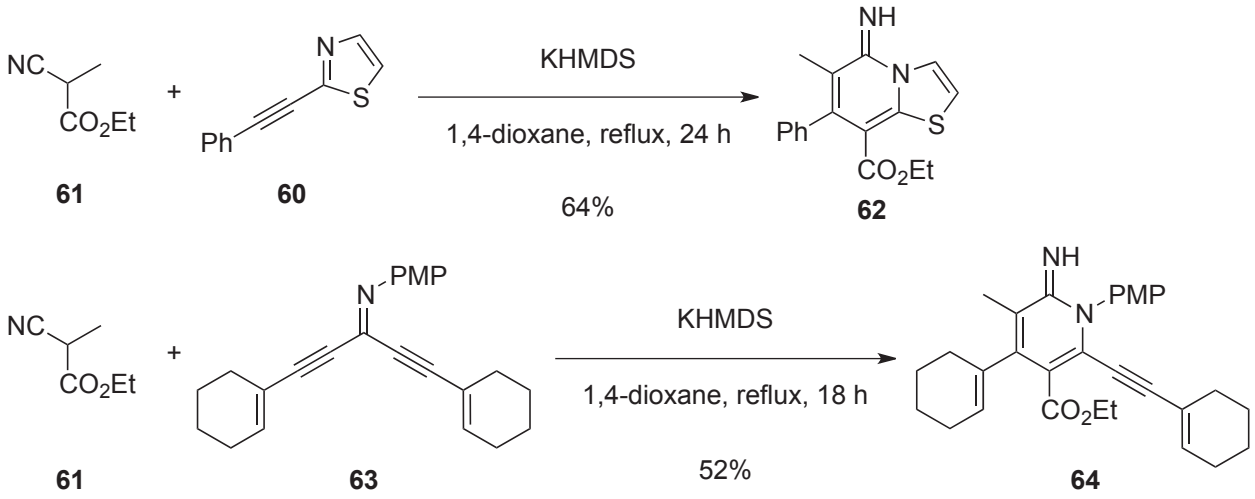
A plausible reaction mechanism is shown in Scheme 11. Metalloenamine **56** would be generated via a conjugate addition of the potassium salt of the cyanoacetate derivative **54** to the alkynyl imine **53** and undergo a chemoselective intramolecular cyclization at the ethoxycarbonyl group to give the cyclobutenoxide intermediate **57**. The cyclobutenoxide **57** would collapse into the metalloenamine **58** via a ring-opening reaction to release the ring strain of the cyclobutene, and subsequent cyclization would

provide the 2-iminopyridine **55** after protonation of the 2-iminopyridine potassium salt **59** with water to quench the reaction.




**Scheme 11.** Plausible Reaction Mechanism for the Synthesis of 2-Iminopyridine **55**

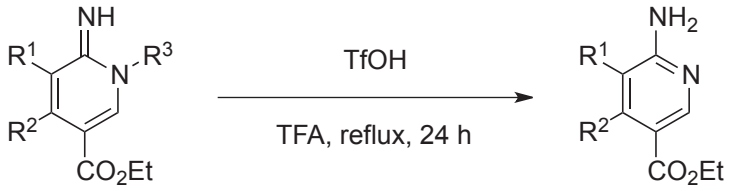
Alkynylthiazole **60** was used instead of alkynyl imines **53** to synthesize a bicyclic compound containing a 2-iminopyridine structure. The reaction of **60** with ethyl 2-cyanopropanoate (**61**) gave the bicyclo-2-iminopyridine **62** in 64% yield. In addition, the synthesis of a 3,4,5,6-tetrasubstituted 2-iminopyridine was carried out. The reaction of dialkynyl imine **63** with **61** gave 2-iminopyridine **64** in 52% yield (Scheme 12).




**Scheme 12.** Synthesis of Bicyclo-2-iminopyridine **62** and 3,4,5,6-Substituted 2-Iminopyridine **64**

The transformation of 2-iminopyridine into 2-aminopyridine was also achieved via the deprotection of substituent at the nitrogen.[31] 2-Aminopyridines are one of the most important heterocycles because of

their biological activity.[32] Deprotection of the *p*-methoxyphenyl group of 2-iminopyridine **55** ($R^3$ = PMP) was attempted under several reaction conditions. However, the desired 2-aminopyridine **65** was not obtained. Trifluoromethanesulfonic acid (TfOH) was found to promote the deprotection of 2-iminopyridine **55** ($R^3$ = MPM) in trifluoroacetic acid (TFA) under reflux, to give the desired 2-aminopyridine **65** in moderate to good yields (Scheme 13).




**55** **65**

$R^1$ = Me, $R^2$ = Ph, $R^3$ = MPM: 70%
$R^1$ = Me, $R^2$ = Bu, $R^3$ = MPM: 59%
$R^1$ = Ph, $R^2$ = Ph, $R^3$ = MPM: 62%

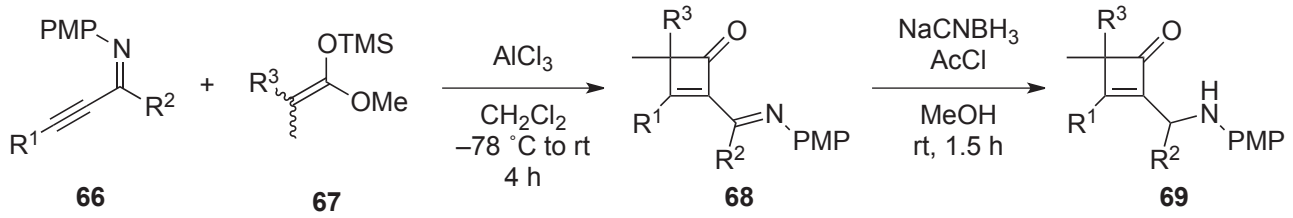
**Scheme 13.** Synthesis of Multi-substituted 2-Aminopyridines **65**

### 3-4. Stereodivergent Synthesis of Both *cis*- and *trans*-*β*-Lactams[33]

New synthetic routes to *β*-lactams are of great importance for structure-activity relationship studies and the development of new derivatives of *β*-lactam antibiotics. *β*-Lactams are also used as versatile building blocks.[34] It has been recognized that the stereochemistry at the C-3 and C-4 carbons of the *β*-lactam ring is involved in the manifestations of biological activity.[35] The Staudinger reaction, enolate-imine condensations, and the cyclization of *β*-amino acids or esters have been used for stereocontrolled construction of the C-3 and C-4 carbons of *β*-lactams.[36] Although numerous methods for the stereoselective synthesis of *cis*- and *trans*-*β*-lactams have been reported, a single-step synthesis has been highly desired from the same precursor. During our investigations involving alkynyl imines, it was envisioned that iminocyclobutenones would be useful intermediates for the synthesis of nitrogen-containing heterocycles via thermal rearrangement of the cyclobutenone ring.[37]

The conjugate addition of alkynyl imines **66** with ketene silyl acetals **67** in the presence of aluminum chloride proceeded to give iminocyclobutenones **68** (Table 8). Alkynyl imines possessing heteroaromatic or aromatic groups as the $R^2$ substituent underwent conjugate addition reactions to give the corresponding iminocyclobutenones **68** in good to high yields (entries 1–4). The reaction of alkynyl imines **66** with the ketene silyl acetal **67** possessing an ethanesulfenyl group gave iminocyclobutenones **68** in good yields (entries 6 and 7).

**Table 8.** Synthesis of Iminocyclobutenones **68** and Aminocyclobutenones **69**




**66** **67** **68** **69**

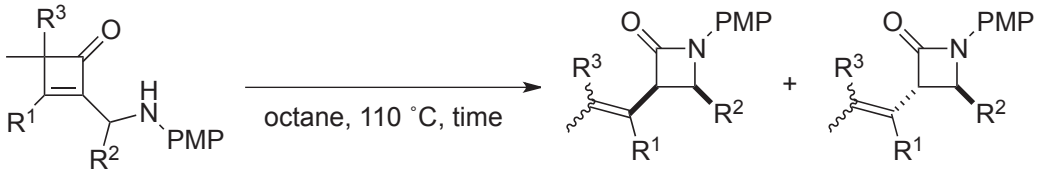
| Entry | $R^1$ | $R^2$ | $R^3$ | Yield of **68** (%) | Yield of **69** (%) |
|---|---|---|---|---|---|
| 1 | Ph | Ph | Me | 82 | 95 |
| 2 | Ph | 2-furyl | Me | 85 | 67 |
| 3 | Ph | 2-naphthyl | Me | 80 | 79 |
| 4 | Ph | 2-thienyl | Me | 71 | 78 |
| 5 | 2-naphthyl | Ph | Me | 75 | 90 |
| 6 | Ph | Ph | SEt | 78 | 89 |
| 7 | Ph | 2-naphthyl | SEt | 83 | 84 |

We carried out the chemoselective reduction of the iminocyclobutenones **68** possessing three reducible functional groups, such as imino, carbonyl, and alkenyl substituents. When sodium cyanoborohydride was used as a reducing reagent, the reduction of iminocyclobutenones **68** in methanol in the presence of acetyl chloride, which reacted with methanol to generate in situ a limited amount of hydrogen chloride, proceeded chemoselectively at room temperature to give the desired aminocyclobutenones **69** in moderate to high yields (Table 8).

Thermal rearrangement of the aminocyclobutenones **69** in toluene or octane at 110 °C proceeded to give the desired *β*-lactams **70** in moderate to good yields, and with good *cis*-selectivities (Table 9).

A plausible reaction mechanism for the thermal rearrangement of the aminocyclobutenones **69** into the *β*-lactams **70** is shown in Scheme 14. Aminoketene **71** would be generated by the ring opening of aminocyclobutenone **69** and undergo cyclization to give the enol intermediate **72**. Protonation of the enol intermediate **72** would occur predominantly from the less hindered face of the enol, to give the *cis*-*β*-lactam **70**.

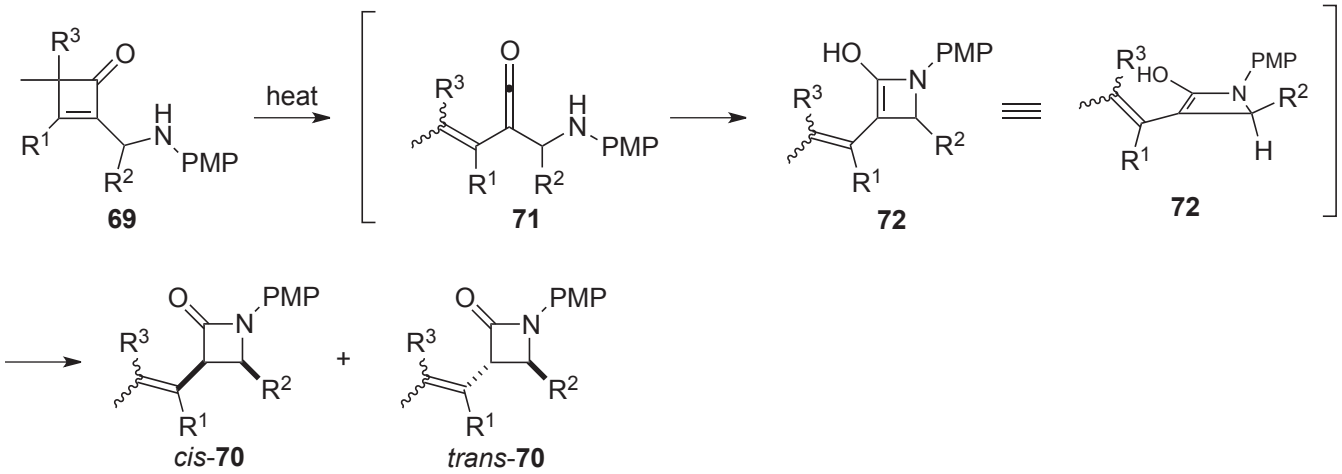
**Table 9.** Thermal Rearrangement of Aminocyclobutenones **69** into *β*-Lactams **70**




**69** *cis*-**70** *trans*-**70**

| Entry | $R^1$ | $R^2$ | $R^3$ | Time (h) | Yield (%) | *cis*/*trans* |
|---|---|---|---|---|---|---|
| 1[a] | Ph | Ph | Me | 24 | 61 | 80/20 |
| 2 | Ph | 2-furyl | Me | 45 | 76 | 74/26 |
| 3 | Ph | 2-naphthyl | Me | 40 | 69 | 75/25 |
| 4 | Ph | 2-thienyl | Me | 48 | 89 | 79/21 |
| 5 | 2-naphthyl | Ph | Me | 48 | 51 | 79/21 |
| 6 | Ph | Ph | SEt | 48 | 65 | 80/20 |

[a] Reaction performed in toluene.

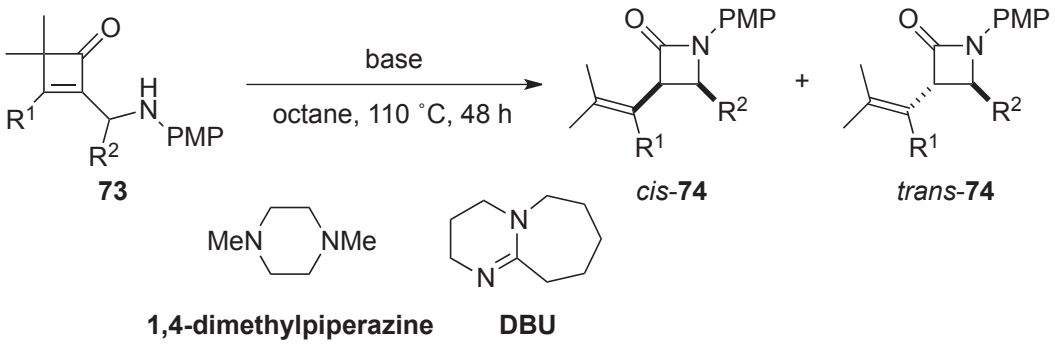



**69** **71** **72** **72** *cis*-**70** *trans*-**70**

**Scheme 14.** Plausible Mechanism for the Thermal Rearrangement

The protonation step is crucial in determining the *cis*-selectivity. Therefore, several additives were investigated in the thermal rearrangement of aminocyclobutenones **73**. Among the additives tested, 1,4-dimethylpiperazine was found to be the most effective regarding both the *cis*-selectivity and yield (Table 10, entries 1–5). On the other hand, thermal rearrangement in the presence of a stronger base, DBU, gave the *β*-lactam **74** with *trans*-selectivity (Table 10, entries 6–10).

**Table 10.** Diastereoselective Synthesis of $\beta$-Lactams **74**




| Entry | Base | $R^1$ | $R^2$ | Yield (%) | *cis*/*trans* |
|---|---|---|---|---|---|
| 1[a] | 1,4-dimethylpiperazine | Ph | Ph | 80 | 98/2 |
| 2 | 1,4-dimethylpiperazine | Ph | 2-furyl | 99 | 82/18 |
| 3 | 1,4-dimethylpiperazine | Ph | 2-naphthyl | 93 | 97/3 |
| 4 | 1,4-dimethylpiperazine | Ph | 2-thienyl | 77 | 94/6 |
| 5 | 1,4-dimethylpiperazine | 2-naphthyl | Ph | 85 | 95/5 |
| 6[a] | DBU | Ph | Ph | 78 | 3/97 |
| 7 | DBU | Ph | 2-furyl | 80 | 2/98 |
| 8 | DBU | Ph | 2-naphthyl | 59 | 2/98 |
| 9 | DBU | Ph | 2-thienyl | 59 | 2/98 |
| 10 | DBU | 2-naphthyl | Ph | 75 | 3/97 |

[a] Reaction performed in toluene.

## 4. CONCLUSION

The 1,4- and 1,2-double nucleophilic addition studied here provides a new entry into reactions using $\alpha,\beta$-unsaturated aldimine as a good acceptor of two types of nucleophiles in one pot. In particular, the use of an $\alpha,\alpha$-dialkoxy ketene silyl acetal, an acyl anion equivalent as the first nucleophile, provides a facile approach to 2,3,5-trisubstituted pyrroles in a regioselective manner. The synthetic utility of this methodology is realized in the construction of various types of pyrroles, in particular the IGPDI. For the reaction with *N*-allylideneamine, the use of a ketene silyl thioacetal as the first nucleophile in the presence of dried silica gel provides the cyclized $\delta$-lactam in high yield.

In addition, we found an intriguing heterocycle synthesis based on the nucleophilic addition of active methine compounds to alkynyl imines. Varying the active methine compounds leads to a specific approach to otherwise non-trivial heterocycles. When a transannular migration of the carbonyl group is involved, this methodology offers a Grob-type fragmentation reaction leading to ring-expansion products involving bicyclo-2-pyridones in a chemoselective manner. The stereodivergent synthesis of

both *cis*- and *trans*-β-lactams was also discovered using the following three crucial reactions: the iminocyclobutenone formation, chemoselective reduction of the imino groups, and thermal rearrangement of the aminocyclobutenones. In this route, the key synthetic intermediates: the iminocyclobutenones were readily synthesized in good yields via the conjugate addition of alkynyl imines with ketene silyl acetals. These new reactions provide new and easy access to nitrogen-containing molecules that are important synthetic intermediates for many bioactive compounds.

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