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STUDIES ON SYNTHESES OF POLYFUNCTIONALIZED PYRIDINE DERIVATIVES

(多官能ピリジン誘導体の合成に関する研究)

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OSAKA UNIVERSITY

1991

PREFACE

The studies presented in this thesis have been carried out under the guidance of Professor Yoshiki Ohshiro at Department of Applied Chemistry, Faculty of Engineering, Osaka University.

I would like to express my sincerest gratitude to Professor Yoshiki Ohshiro for his constant guidance, helpful suggestions and hearty encouragement throughout this work.

It is a great pleasure to express my hearty acknowledgements to Associate Professor Mitsuo Komatsu for his intimate guidance, kind encouragement, stimulating discussions, and continuous advices.

I wish to thank Dr. Toshikazu Hirao and Dr. Shinobu Itoh for their valuable discussions and helpful suggestions. I also thank Associate Professor Yoshiaki Inaki for his encouragement and kind advices.

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Further, I wish to thank all other members of research group of Professor Yoshiki Ohshiro for their occasional discussions and helpful cooperations.

Finally, I would like to thank my parents and my sister for their hearty encouragement and assistance.

Suita, Osaka
January 1991

Nagatoshi Nishiwaki

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GENERAL INTRODUCTION

In recent years, biologically active compounds and functional materials have been drawing much attention and the basic research for them are in keen need both in academic and industrial fields. Heterocyclic compounds containing pyridine ring are not only the fundamental skeletons of the biologically active compounds but also utilized for medicines, agrochemicals, and their synthetic intermediates.[1] Thus they would be one of the important targets in organosynthetic chemistry and in fine chemicals industries. Among them, polyfunctional pyridines are the important key compounds for the development of functional heterocyclic systems containing nitrogen atoms. However, effective synthetic methods of such compounds have been less known because of difficulty in substitution on pyridine ring. Hence it is strongly desired to develope the facile methods to introduce the functional groups to the pyridine ring.

From this point of view, the introduction of ethynyl groups to pyridine ring was studied focusing on their versatile reactivities. Since ethynylated pyridine skeleton has both characters of pyridine ring and of acetylene, ethynylpyridines are utilized for various purposes.

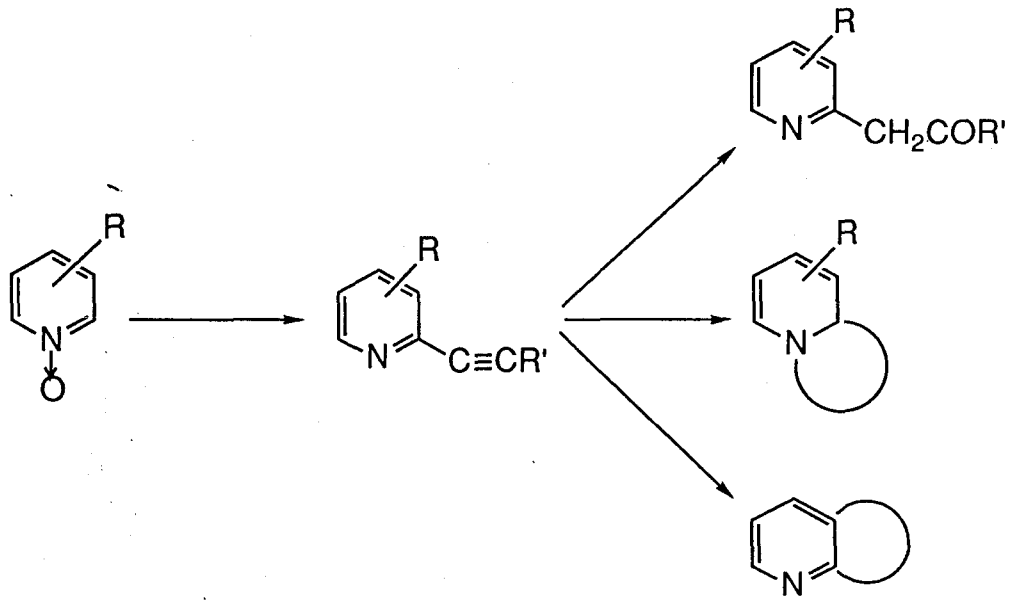
For example, they are used as synthetic intermediates of bicyclic pyridines[2),3)] and natural products.[4),5)] In addition, pharmacological activity of ethynylpyridine was screened as an analog of ergonovine[6)] and biological activity of ethynylpyridoxol was also studied as a modified vitamin B_6.[7)] While there are reports where ethynylpyridine was utilized for π-conjugated polymer[8)] or chiral smectic liquid crystalline compound.[9)]

Although ethynylpyridines are widely employed as mentioned above, there are not further applications because it is very difficult to synthesize functionalized ethynylpyridines. Thus development of facile ethynylation method of functionalized pyridines is highly valuable.

Furthermore, chemical transformations of obtained ethynylpyridines were investigated to give novel polyfunctionalized pyridines. As a results of these studies, possibility of transformation of ethynylpyridines to functionalized phenacylpyridines and bicyclic pyridines was established.

Phenacylpyridines[10] and indolizine derivatives[11] are applied to various functional materials such as biologically active compounds, dyes and synthetic intermediates of polycyclic systems, but easy functionalizing methods of these compounds having functional group are not known.

[*b*]-Fused pyridines are pharmacologically interesting compounds and most of them are synthesized from vicinally bifunctionalpyridines. Thus 3-functionalized ethynylpyridines are useful for syntheses of bicyclic pyridines.[12] With reference to this subject, Yamanaka *et al.* actively investigated utilization of ethynylpyridines.[13] However, there are many problems in terms of the difficulty of starting materials and the restrictions of substituents and of reaction conditions. Hence, development of ready synthetic methods to obtain bicyclic pyridines is desired.



With these backgrounds, syntheses of polyfunctionalized pyridine derivatives were investigated. In Chapter 1, the regioselective direct ethynylation of the

pyridines by use of Reissert-Henze type reaction is described. In Chapter 2, the synthesis of functionalized phenacylpyridines by hydration or oxidation of ethynylpyridines is stated. Chapter 3 deals with synthesis of indolizines, representative ring system of [*a*]-fused pyridines and the pH sensitive behavior of the oligomer of the indolizine derivatives. In Chapter 4, syntheses of various [*b*]-fused pyridines by intramolecular cyclization of ethynylpyridines are described.

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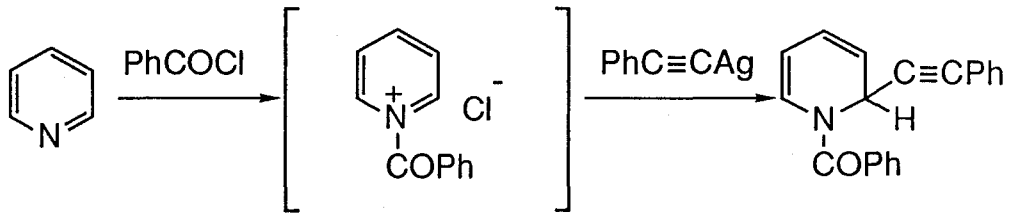
CHAPTER 1. ETHYNYLATION OF PYRIDINES BY REISSERT - HENZE TYPE REACTION

1-1. Introduction

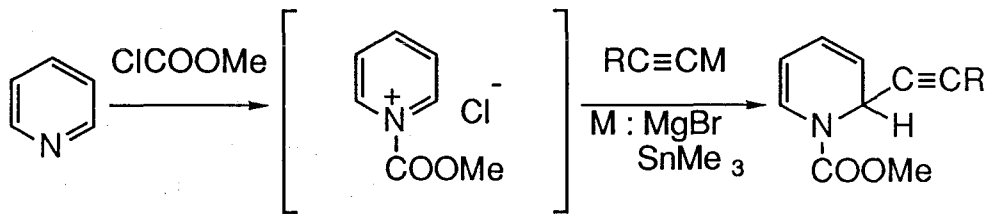
Polyfunctionalized pyridines are useful for functional materials or their synthetic intermediates. For example, they are used for medicinal, agricultual, photographic, or conductive materials. Thus it is of great importance to develop facile methods for introducing functional groups to a pyridine ring in terms of synthesis of polyfunctionalized pyridines. Especially introduction of an ethynyl group possessing versatile reactivity is highly valuable, but the known direct ethynylation methods suffer from some restrictions.

Method A



(Agawa)[1]

Method B

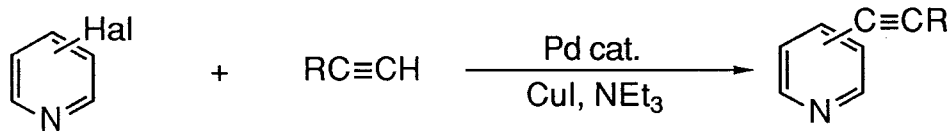


(Kawanisi)[2]
(Utimoto)[3]

Products according to the methods of the Reissert type ethynylation reaction (Methods A and B), are dihydropyridines, which are often used for alkaloid

syntheses. Although the aromatization methods[6,7] of alkylated dihydropyridines are known, there are few methods of aromatization of ethynylated dihydropyridines.[1] Hence, the methods A and B are not applicable to synthesis of ethynylpyridines.

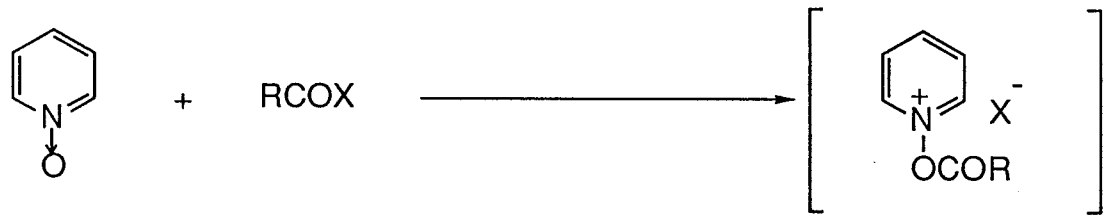
Method C



(Hagihara)[4]
(Yamanaka)[5]

The palladium catalyzed coupling reaction (Method C) is an excellent synthetic method for ethynylpyridines, but it is necessary to obtain functionalized halopyridines as starting materials. Since the halopyridines are not always easily available, this method is unsuitable for synthesis of functionalized ethynylpyridines.

In this chapter, attention was paid to the Reissert-Henze salt, an *N*-acyloxypyridinium salt, bearing a good leaving group, and the nucleophilic reactions of an acetylide toward the salt was carried out to ethynylate pyridines directly. Furthermore, the present reaction was applied to the substituted pyridines, to pyridine homologs and also to several types of acetylenes.



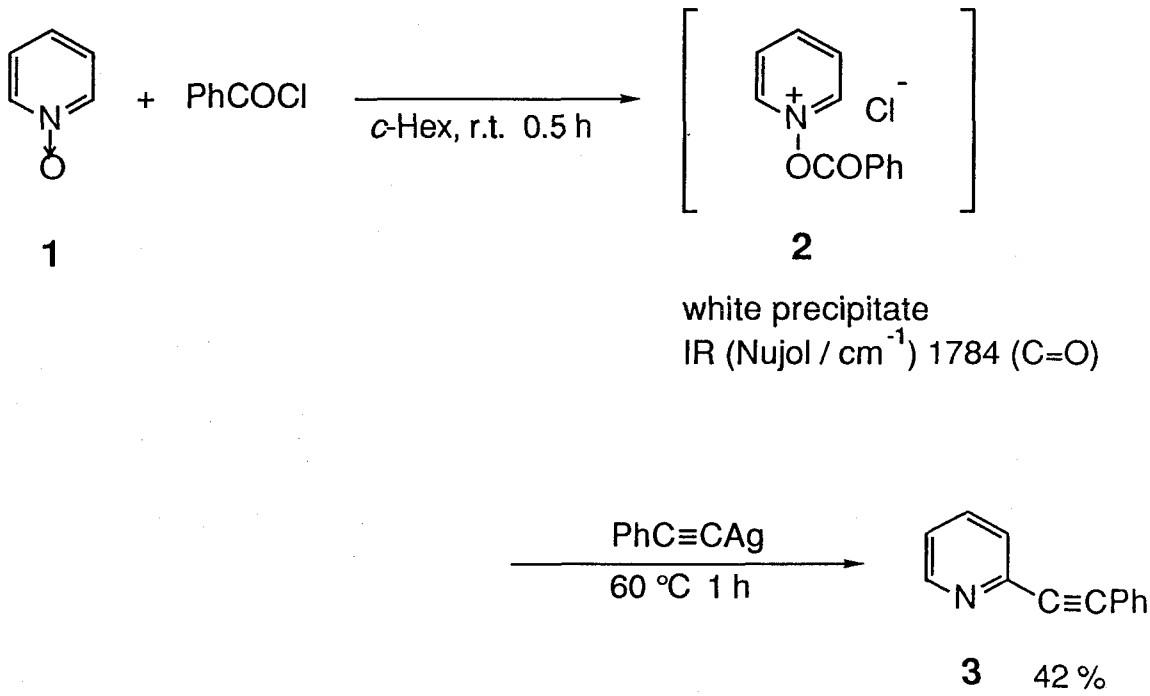
Reissert-Henze salt

1-2. Results and Discussion

1-2-1. Reissert-Henze Type Ethynylation of Pyridine

To a cyclohexane solution of pyridine *N*-oxide (**1**), benzoyl chloride was added to generate *N*-benzoyloxypyridinium chloride (**2**) immediately as white precipitates at room temperature. It was possible to isolate the salt **2** under nitrogen atomosphere and its structure was confirmed by observation of absorption of carbonyl group at 1784 cm^{-1} (Nujol) in the IR spectrum. However, as this salt is too hygroscopic and decompose readily,[8] it was used without isolation for the following ethynylation reaction.

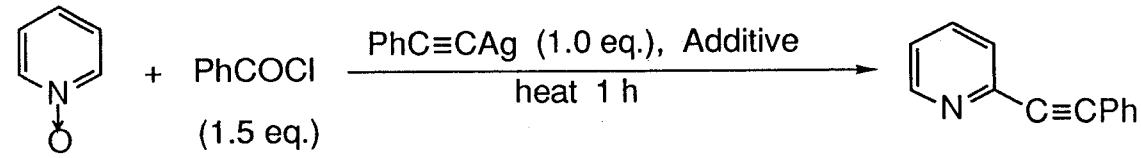
The Reissert-Henze salt **2** was heated with silver phenylacetylide to give 2-phenylethynylpyridine (**3**) in 42 % yield, which was a directly ethynylated product. In the present reaction, the ethynylation selectively occurred at 2-position (α-position), and 4-phenylethynylpyridine, the γ-ethynylated product, was not detected at all.



1-2-2. Studies on Reaction Conditions

The reaction conditions, solvents e.g. reaction temperature, time, and additives, were examined. The results are shown in Table 1.

Table 1.



(1.5 eq.)

Solv.	Temp. (°C)	Time (h)	Additive	Yield (%)[a)]
PhH	80	1	–	35
PhMe	110	"	–	33
c-Hex	80	"	–	40
"	60	"	–	41
"	"	5	–	43
"	40	1	–	22
"	rt (27)	"	–	2
n-Hex	60	"	–	45
THF	"	"	–	27
$CHCl_3$	"	"	–	36
DMF	"	"	–	5
DMSO	"	"	–	0
c-Hex	"	"	NEt_3 [b)]	46
"	"	"	DBU [b)]	trace
"	"	"	Na_2CO_3 [c)]	13

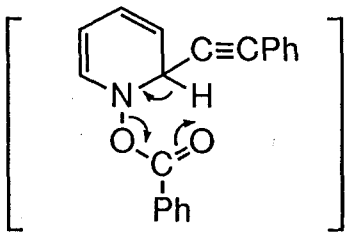
a) by ^{1}H-NMR b) 1.5 equiv. c) 10 equiv.

Nonpolar solvents including hexane, cyclohexane and benzene, were more suitable than polar solvents. In the case of polar solvents, side reactions such as

ring opening reaction occurred. Although the reaction mixture containing Reissert-Henze salt and silver acetylide was easily soluble in *N,N*-dimethylformamide (DMF), little ethynylpyridine was obtained but *N,N*-dimethylbenzamide which derived from DMF itself. When dimethylsulfoxide (DMSO) was used as a solvent, the ethynylation did not proceed. It was thought the salt **2** was not formed due to the comlexation of DMSO to *N*-oxide **1**.[9,10] In the case of chloroform, which was frequently used as a solvent for similar reactions, the salt **2** was readily dissolved but only similar reactivity in cyclohexane was observed.

The reaction was performed at 60 through 80 °C for 1 h, and higher temperature or prolonged reaction time caused no positive effect.

It is supposed that the reaction proceeds with attack of the acetylide to the pyridine ring to form 1,2-dihydropyridine intermediate **4** followed by elimination of benzoic acid. Bases were added in order to accelerate the elimination of the proton at 2-position from the adduct **4** and to trap benzoic acid, but no effect appeared. Thus the elimination of benzoic acid from **4** is considered to proceed intramolecularly.



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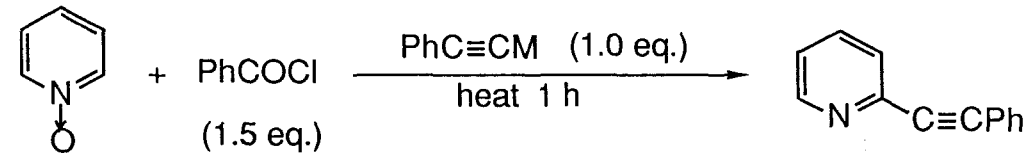
1-2-3. Studies on Metals of Acetylides

Comparison of metals of acetylides was also studied (Table 2). When a copper acetylide and a Grignard reagent were used, ethynylation of pyridine occurred in lower yields than that with silver acetylide. In the case of a sodium or a lithium acetylide, a more ionic acetylide, benzoyl(phenyl)acetylene was obtained as a result of their attack to the benzoyloxy moiety[2] not to pyridine ring of **4**. This reaction of sodium acetylide proceeded even at -78 °C and ethynylpyridine **3** was not detected.

Trimethylsilyl[11] or trimethyltin[11,12] phenylacetylide did not give the ethynylpyridine **3** and phenylacetylene was recovered after workup.

Table 2



(1.5 eq.)

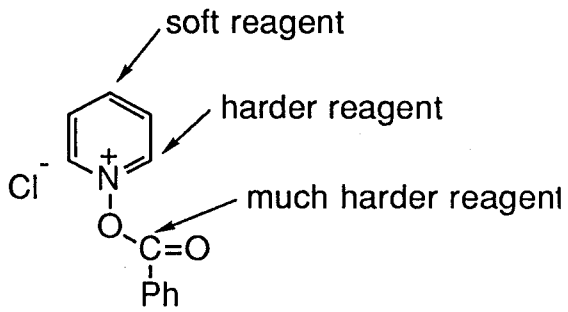
M	Solv.	Temp. (°C)	Yield (%)[a]
Ag	PhH	80	35
"	*c*-Hex	60	42
Cu	PhH	80	10
Na	"	"	0 [b]
"	*n*-Hex	-78	0 [b]
Li	"	"	0 [b]
MgBr	*c*-Hex	60	21
$SiMe_3$	"	"	0 [c]
$SnMe_3$	"	"	0 [c]

a) by ^{1}H-NMR
b) PhCOC≡CPh was obtained.
c) PhC≡CH was recovered.

It was suggested by Akiba[13] that the regioselectivity of nucleophilic attack to the pyridine ring could be explained by the HSAB principle. Namely, the soft nucleophilic reagent attacks the 4-position, the softer position, and the hard one attacks the 2-position, the harder position. In addition, it was reported that alkynyl

magnesium bromide attacked at 2-position of pyridine selectively in the Reissert type reaction.[2] Hence, in the present reaction, silver acetylide selectively attacked at 2-position of the Reissert-Henze salt similarly to the above cited reactions.

On the other hand, much harder reagents (sodium and lithium acetylides) attacked the benzoyl carbon, the hardest position in the salt. Thus sodium or lithium acetylide is too hard to attack the pyridine ring and silver acetylide is the most suitable nucleophilic reagent which has the moderate hard character. The ethynylation in higher yields or the ethynylation at 4-position would be possible, if more proper metal acetylides are employed.



1-2-4. Studies on Salt Forming Agents

As salt forming reagents, various types of acyl halides were examined. The results were summarized in Table 3.

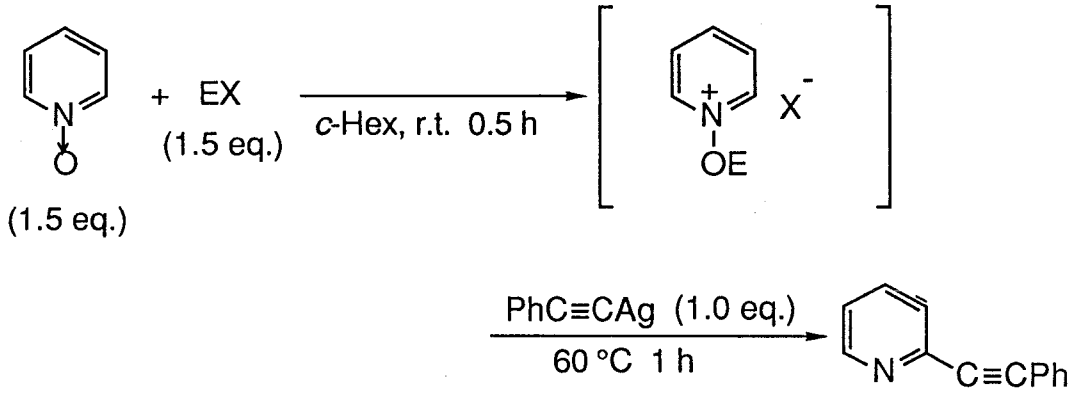
Benzoyl bromide showed similar reactivity to that of benzoyl chloride. Benzoyl fluoride was not able to form the Reissert-Henze salt even in the solution under reflux, and *N*-oxide and benzoyl fluoride were recovered respectively.

The *p*-substituted benzoyl chlorides were also studied since they were expected to influence on the elimination of acid or the acidity of the proton at 2-position in the 1,2-dihydro intermediate. In the case of *p*-toluoyl chloride, the ethynylpyridine was obtained in a similar yield. While the yield was decreased when *p*-nitrobenzoyl chloride was used because of its low solubility to cyclohexane.

Aliphatic acyl chlorides such as acetyl chloride and pivaloyl chloride were examined. Acetyl chloride showed lower reactivity and steric hindered pivaloyl

chloride gave similar results as that of benzoyl chloride. Benzenesulfonyl chloride also reacted to give ethynylpyridine **3**, but the yield was not improved.

Table 3.

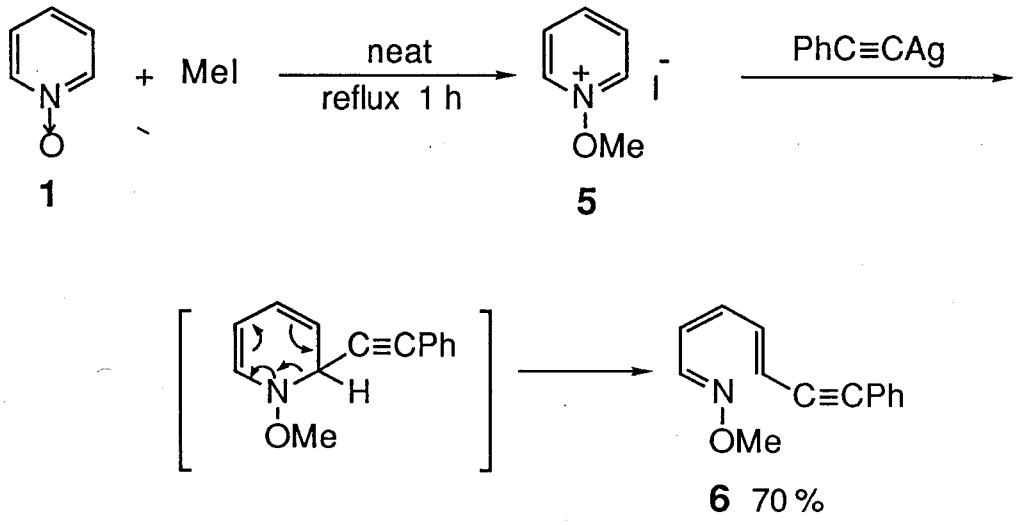


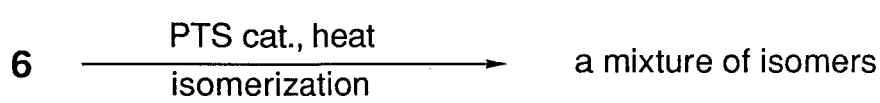
EX	Yield (%) [a)]
PhCOCl	41
PhCOBr	38
p-MeC_6H_4COCl	39
p-$NO_2C_6H_4COCl$	28 [b)]
$PhSO_2Cl$	37
t-BuCOCl	43
MeCOCl	24
$ClCH_2COCl$	3
Ac_2O	0
Me_3SiCl	0
$SnCl_4$	0
$Ti(OPr^i)_4$	0

a) by ^{1}H-NMR b) in PhH

Furthermore, some other salt forming reagents were investigated. Acetic anhydride which is extensively used to form quaternary salt of *N*-oxide gave no ethynylpyridine **3**. In the case with Lewis acids such as trimethylsilyl chloride, tin tetrachloride, and titanium tetraisopropoxide, the ethynylation did not undergo at all.

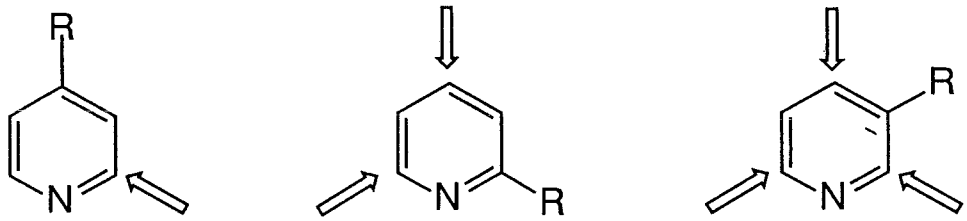
Methyl iodide did not form the corresponding quaternary salt under the conditions used for the acyl halides, but the salt was prepared by the known method.[14] Reaction of the isolated *N*-methoxypyridinium iodide (**5**) with silver phenylacetylide gave the acyclic product **6**[9] and no ethynylated pyridine. The similar ring opening reaction using aryl magnesium bromide was also reported.[15] It is probably due to difference in character of the leaving group; namely, elimination of methanol is so slow in comparison with benzoic acid that ring opening of the intermediate becomes exclusive. Although ring closure of the azatriene **6** was examined by heating in the presence of *p*-toluenesulfonic acid, only isomerization of **6** occurred.





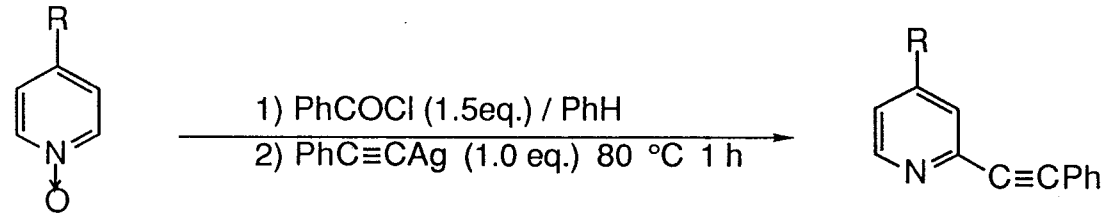
1-2-5. Application for Substituted Pyridines

In order to synthesize polyfunctionalized pyridines, the present method was applied to substituted pyridine *N*-oxides. When substituted *N*-oxides were employed in this ethynylation, a few points should be considered through the reactions; the side reaction on reactive substituents, the regioselectivity of ethynylation at 2-, 4-, or 6-positions, and the effects of the substituent on reactivity and selectivity of ethynylation.



a) Ethynylation of 4-Substituted Pyridine *N*-Oxides

At first, ethynylation of the 4-substituted pyridine *N*-oxides. Since these substrates are symmetoric, the ethynylation occurred only at 2-position to give ethynylpyridines **7**, **8**, and **9**. It is noteworthy that the present reaction is applicable to the pyridine *N*-oxides possessing reactive functional groups such as acetyl, cyano, etc. Although most of these functionalized ethynylpyridines are hitherto unknown or difficult to be synthesized, they could be readily prepared by our method.



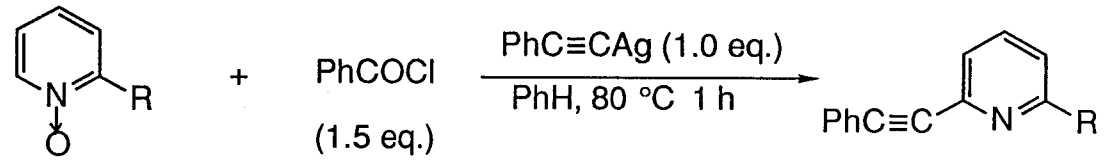
(1.5 eq.)

R=	Me	**7**	25 %
	CN	**8**	50 %
	Ac	**9**	51 %

In this ethynylation reaction, electron-withdrawing substituents raised the yields of ethynylpyridines, but the electron-releasing substituent gave the opposite result.

b) Ethynylation of 2-Substituted Pyridine *N*-Oxides

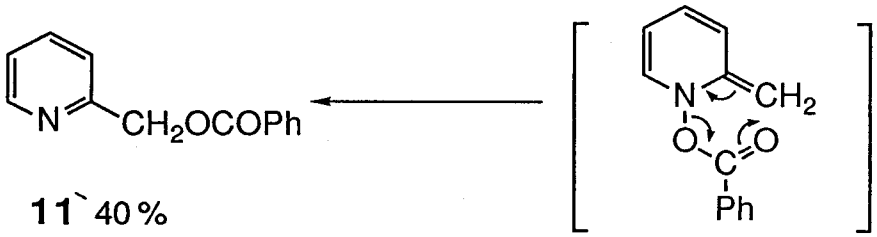
Ethynylation of 2-substituted pyridine *N*-oxides were then examined. It is possible for the acetylide to attack at 4- and 6-positions, but only 6-ethynylated pyridines **10**, **12** were obtained.



(1.5 eq.)

R = Me **10** 30 %[a)]
Ac **12** 50 %

a) Ester **11** was obtained in 40 % yield.

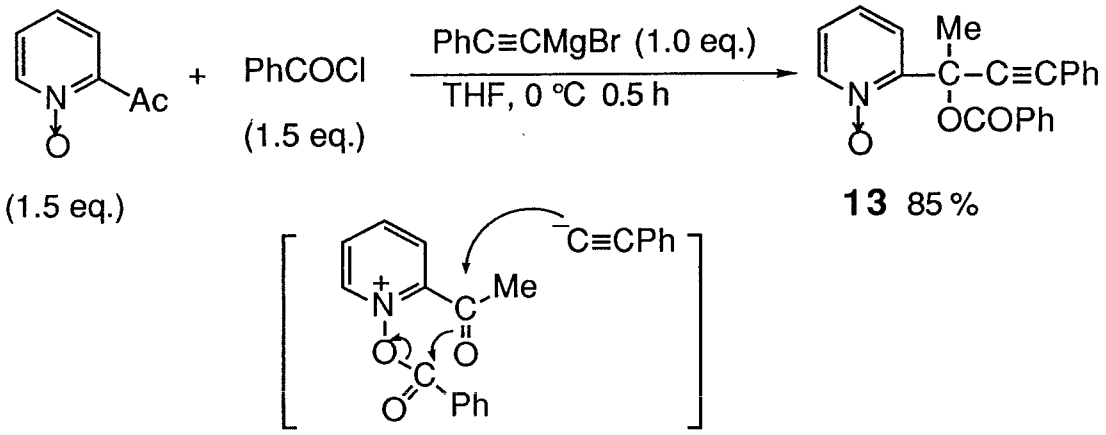


11 40 %

In the case of 2-methylpyridine *N*-oxide, rearrangement of benzoyloxy group to methyl group mainly underwent to give the ester **11**.[16)] This rearrangement is thought to be one of the reasons for the low yield of ethynylpyridine **10**.

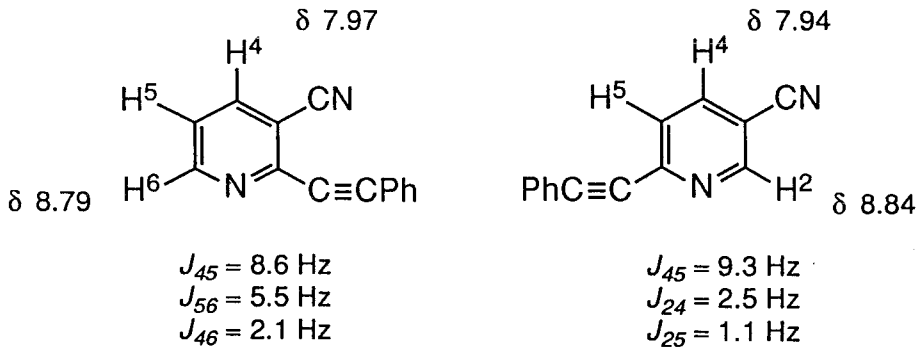
2-Acetyl derivative similarly gave the 6-ethynylated pyridine **12** in a moderate yield. When the phenylethynyl magnesium bromide was used instead of silver acetylide, the ethynylated product was not **12** but the *N*-oxide **13** which was ethynylated at acetyl group in 85 % yield. This result shows that silver acetylide is

the more suitable reagent for syntheses of functionalized ethynylpyridines in the present reaction.



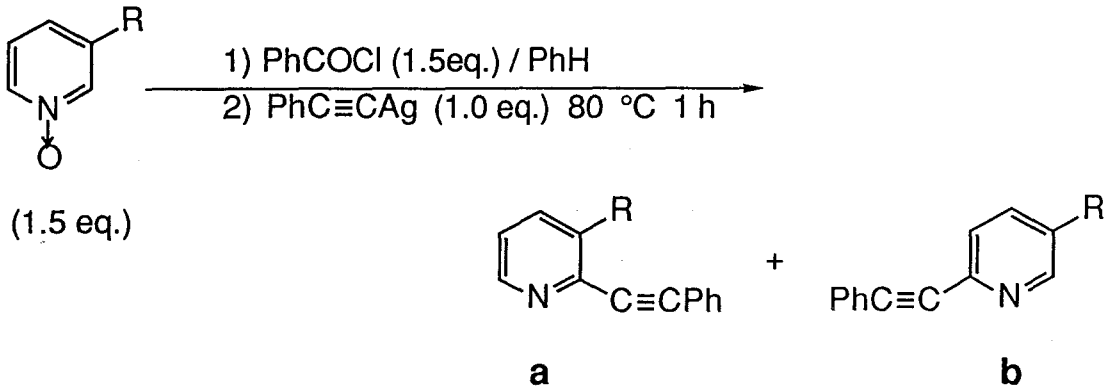
c) Ethynylation of 3-Substituted Pyridine *N*-Oxides

Finally, the ethynylation of 3-substituted pyridine *N*-oxides were studied. The ethynylation occurred at 2- and 6-positions but not at 4-position. The structure of each isomer was determined by coupling constants in ^{1}H-NMR spectra. One Examples of spectral data are shown below.



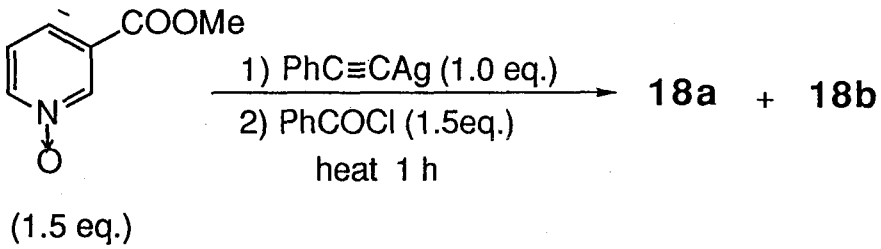
Similarly to the results mentioned in the sections **a** and **b**, the yields of ethynylpyridines bearing electron releasing-groups were lower than those of the pyridines bearing electron-withdrawing ones. On the other hand, the ethynylation

at the 2-position was predominant in all cases.[17] In contrast, *N*-oxides substituted by methyl or ethyl groups gave 2-ethynylated products more selectively than *N*-oxides substituted by electron-withdrawing groups.



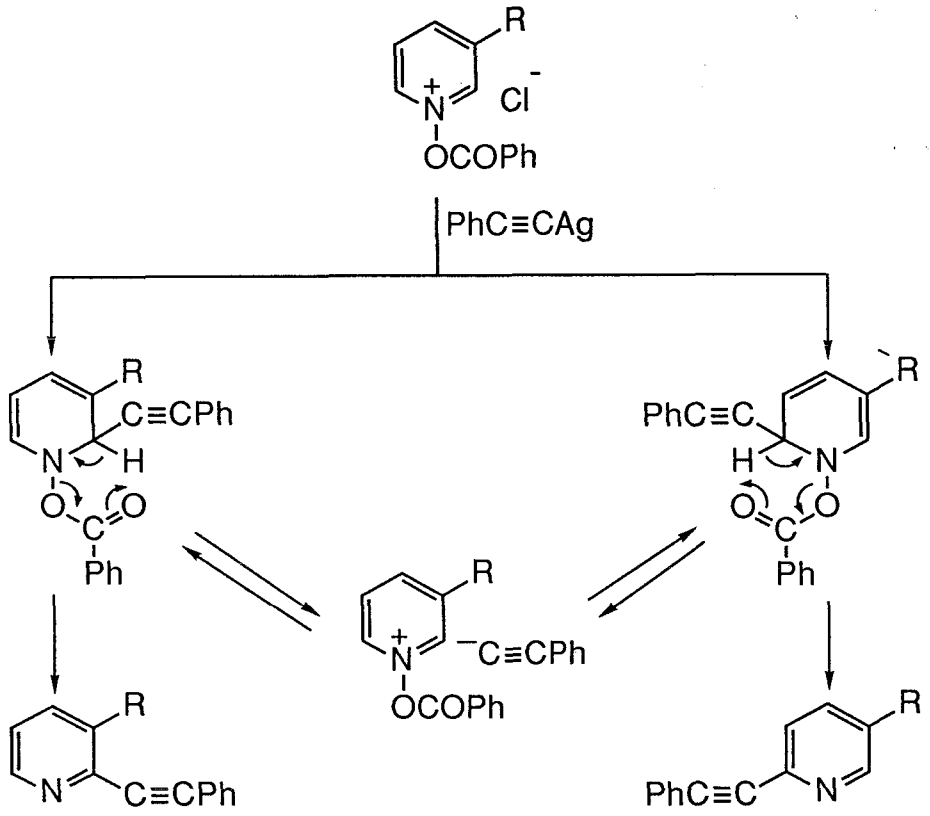
	R	Total Yield (%) [a]	**a** : **b** [a]
14	Me	39	83 : 17
15	Et	36	70 : 30
16	COMe	47	67 : 33
17	CN	60	56 : 44
18	COOMe	58	48 : 52

a) by ^{1}H-NMR



Solv.	Temp. (°C)	Total Yield (%)	**18a** : **18b**
c-Hex	60	26	17 : 83
c-Hex	80	40	29 : 71
PhH	80	47	52 : 48
THF	67	26	65 : 35
dioxane	80	30	74 : 26

The effects of reaction conditions on the regioselectivity of ethynylation at 2- or 6- positions were studied. Higher reaction temperature and higher polarity of solvents gave rise to higher regioselectivity of the 2-substituted pyridines.



The regioselectivity is associated with electronic and steric factors. When pyridine *N*-oxides bearing an electron-withdrawing substituent are used, silver acetylide, the less hard reagent, attacks the 6-position, the less hard position, predominantly. However, since the proton at 2-position of 1,2-adduct is more acidic than that of 1,6-adduct and there is more strong steric repulsion in the 1,2-adduct. Hence, the aromatization of 1,2-adduct occurred faster than that of 1,6-adduct, and 2-ethynylated pyridine is obtained in larger yield than that of the 6-ethynylated pyridine. On the other hand, when *N*-oxides bearing the electron-releasing group

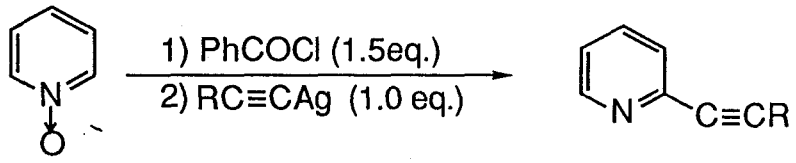
are used, the acetylide attacks the 2-position to give 1,2-adduct and successively aromatized to give 2-ethynylpyridine with high selectivity.

The contribution of the formation of 1,2-adduct is more effective at the higher temperature. The higher polarity of solvent raised the hardness of acetylide and the acidity of the proton at 2-position of 1,2-adduct, thus 2-ethynylated pyridine was produced predominantly.

These reaction pathes cotain some speculatios and the detailed investigation would be needed to clarify them.

1-2-6. Application to Other Acetylenes

This reaction could be applied to other types of acetylenes. Silver acetylides having alkyl, alkoxy or methoxycarbonyl[18] groups reacted with Ressert-Henze salt under similar conditions, and the corresponding ethynylpyridines **19**, **20** and **21** were produced in rather low yields. From these results, the present method is applicable to other acetylides and, hence, the introduction of various substituted ethynyl groups would be expected.



(1.5 eq.)

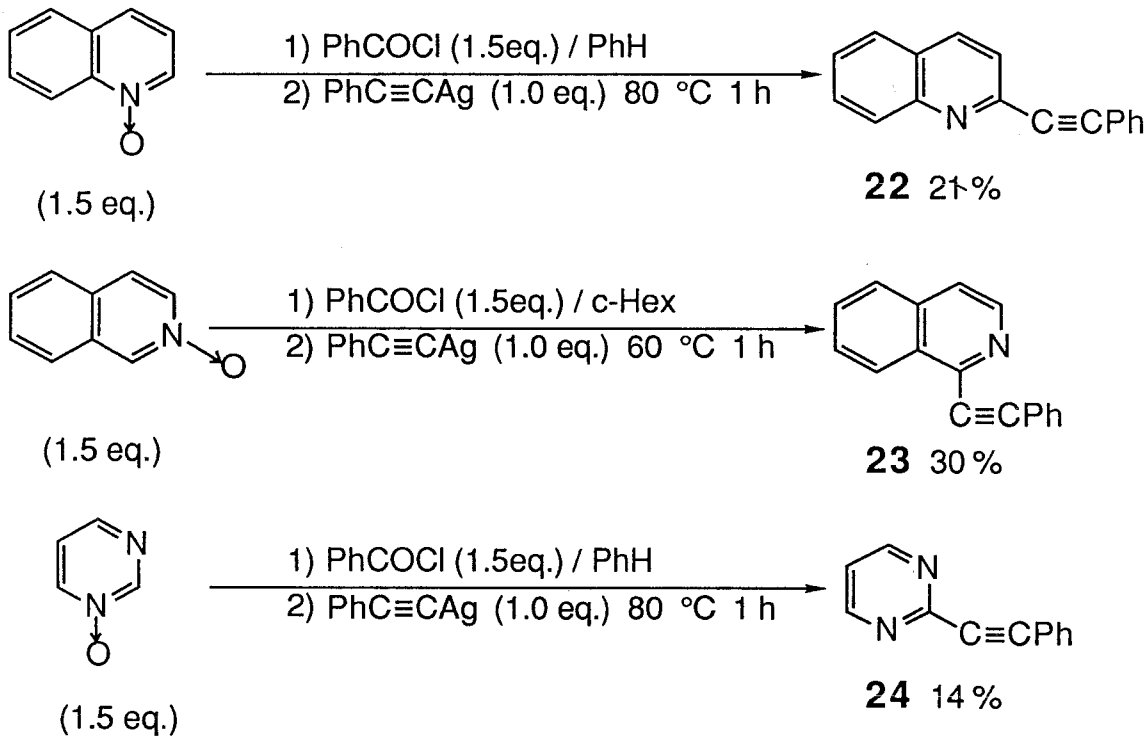
R = *n*-Bu	*n*-Hex, 60 °C 1 h	**19**	20 %
R = CH_2OTHP	PhH, 80 °C 1 h	**20**	22 %
R = COOMe	PhH, 80 °C 1 h	**21**	20 %

(THP : tetrahydropyranyl)

1-2-7. Application to Pyridine Homologs

Application of this method to *N*-oxides of other pyridine homologs was also possible. In each case, ethynylation occurred only at α-position of the nitrogen atoms to give ethynylated homolgs.

Quinoline *N*-oxide gave the correspoding ethynylated quinoline **22**. Isoquinoline *N*-oxide similarly gave 1-ethynylated isoquinoline **23** but 3-ethynylated one was not obtained. In this case, aromaticity of benzene ring of 1,2-dihydro intermediate is not broken while that of 2,3-dihydro intermediate must be broken. Hence, the ethynylation is considered to proceed only at 1-position. Pyrimidine 1-oxide gave the 2-ethynylated pyrimidine **24**, but 6-ethynylated one was not detected.



As mentioned above, although the reaction conditions should be optimized to get better yields, the most important nature of this reaction is applicability to various acetylenes and wide range of pyridines including those having reactive substituents such as acetyl group.

1-3. Experimental

General

Melting points are uncorrected. Mass spectra were obtained using a HITACHI RMU-6E (70 eV) and a JEOL JMS-DX 303 mass spectrometer. IR spectra were recorded on a Hitachi 270-30 infrared spectrometer and NMR spectra were measured on a JEOL FT-NMR JMN FX90Q at 90 MHz with TMS(CH_2)SO_3Na (in D_2O) and TMS (in the other solvents) as an internal standard. Elemental analyses were performed on Yanagimoto CHN-Corder Mt-2.

Preparation of *N*-Oxides

The *N*-oxides were prepared by the oxidation of pyridines with peracetic acid according to the literature method.[19] They were distilled or recrystalized before used.

Preparation of Acetylides

The acetylides were prepared from the corresponding acetylenes according to the literature method.[1]

Typical Procedure of Ethynylation Reaction

Benzoyl chloride (175 μl, 1.5 mmol) was added dropwise to a solution of pyridine *N*-oxide (**1**, 143 mg, 1.5 mmol) in cyclohexane (5 ml) at room temperature to generate *N*-benzoyloxypyridinium chloride (**2**) as white precipitates.[7] After stirring for 0.5 h, silver phenylacetylide (209 mg, 1.0 mmol) was added and the reaction mixture was heated at 60 °C for 1 h. Insoluble material was filtered off and the filtrate was washed with 2 *N* NaOH (10 ml x 4), dried ($MgSO_4$) and concentrated. The residue was chromatographed (Al_2O_3) eluted with hexane/benzene (1/1) to give 2-phenylethynylpyridine (**3**) as yellow oil (76 mg, 42 %).

Other ethynylpyridines were obtained from corresponding *N*-oxides by similar procedure.

2-Phenylethynylpyridine (3)[1)4)] : yellow oil; bp 93-95 °C/0.05 mmHg; IR (neat/cm^{-1}) 2224; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.0-7.8 (m, 8H), 8.62 (ddd, J = 4.5, 1.5, 0.7 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 150.0, 143.5, 135.9, 131.9, 128.8, 128.2, 127.0, 122.6, 122.3, 89.1, 88.6; MS (EI) m/z 179 (100), 178 (35), 151 (7).

2-Phenylethynylpyridinium picrate (3') : yellow plates; mp 153-162 °C; Anal. Calcd. for $C_{19}H_{12}N_4O_7$: C, 55.89; H, 2.96; N, 13.72; O, 27.43. Found: C, 55.76; H, 2.93; N, 13.69.

2-Phenylethynyl-4-methylpyridine (7) : yellow oil (lit.[20)] 105 °C/0.1 mmHg); IR (neat/cm^{-1}) 2216; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.05 (dm, J = 4.8 Hz, 1H), 7.2-7.7 (m, 6H), 8.44 (d, J = 4.8 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 148.6, 146.2, 142.1, 130.8, 127.8, 127.4, 126.9, 122.9, 121.4, 88.1, 87.7, 19.6; MS (EI) m/z 193 (100), 192 (21), 165 (20).

2-Phenylethynyl-4-cyanopyridine (8) : pale yellow needles; mp 87-88 °C; IR (KBr/cm^{-1}) 2240, 2212; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.3-7.9 (m, 7H), 8.86 (dd, J = 5.0, <1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 150.9, 144.7, 132.0, 129.5, 128.4, 128.3, 123.5, 121.2, 120.7, 115.7, 91.9, 87.0; MS (EI) m/z 204 (100), 203 (23), 177 (10), 176 (8); Anal. Calcd. for $C_{14}H_8N$: C, 82.33; H, 3.95; N, 13.72. Found: C, 82.31; H, 3.88; N, 13.43.

2-Phenylethynyl-4-acetylpyridine (9) : pale yellow pastes; mp 86.5-88 °C; IR (KBr/cm^{-1}) 2216, 1698; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.1-7.8 (m, 6H), 7.98 (dd, J = 1.9, <1 Hz, 1H), 8.78 (dd, J = 5.2, <1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.8, 151.1, 144.7, 140.3, 132.0, 129.2, 128.4, 124.8, 121.8, 119.9, 90.4, 88.1, 26.5; MS (EI) m/z 221 (100), 206 (40), 179 (17), 178 (28), 151 (54), 43 (22); Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; O, 7.23. Found: C, 81.24; H, 4.94; N, 6.28.

2-Phenylethynyl-6-methylpyridine (10)[21)] : brown oil; IR (neat/cm^{-1}) 2212; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.0-7.7 (m, 8H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 158.9, 142.7, 136.2, 132.0, 128.7, 128.3, 124.3, 122.5, 88.9, 88.7, 24.5; MS (EI) m/z 193 (100), 192 (18), 178 (7), 165 (14); Anal. Calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.61; H, 5.77; N, 7.22.

2-Pyridylmethyl Benzoate (11) : IR (KBr/cm^{-1}) 1726; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.50 (s, 2H), 7.1-7.9 (m, 6H), 8.0-8.3 (m, 2H), 8.64 (ddd, J = 4.8, 1.7, <1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 166.1, 156.1, 149.5, 136.7, 133.1, 130.0, 129.8, 128.4, 122.8, 121.6, 67.2; MS (EI) m/z 213 (3), 108 (100), 105 (38), 78 (13), 77 (28); Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57; O, 15.00. Found: C, 72.99; H, 5.24; N, 6.55.

2-Phenylethynyl-6-acetylpyridine (12) : pale yellow plates; mp 129-131 °C; IR (KBr/cm^{-1}) 2228, 2204, 1700; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.76 (s, 3H), 7.2-8.1 (m, 8H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 199.2, 153.8, 142.8, 136.9, 132.0, 130.4, 129.1, 128.4, 121.9, 120.4, 89.7, 88.2, 25.6; MS (EI) m/z 221 (100), 193 (28), 179 (91), 178 (46), 151 (19), 43 (26); Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; O, 7.23. Found: C, 81.48; H, 5.12; N, 6.21.

2-Phenylethynyl-3-methylpyridine (14a) : yellow oil (lit.[20] 105 °C/0.1 mmHg); IR (neat/cm^{-1}) 2220; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.54 (s, 3H), 7.0-7.3 (m, 7H), 8.44 (dd, J = 4.8, 1.7 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 147.3, 143.1, 136.9, 135.9, 131.9, 128.8, 128.4, 122.6, 122.6, 93.0, 87.5, 19.4; MS (EI) m/z 193 (100), 192 (57), 165 (18); Anal. Calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.64; H, 5.81; N, 7.41.

2-Phenylethynyl-5-methylpyridine (14b) : colorless needles; mp 84-85 °C; IR (KBr/cm^{-1}) 2210; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.0-7.7 (m, 7H), 8.44 (dd, J = 1.9, <1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 150.6, 140.7, 136.6, 132.6, 132.0, 128.7, 128.3, 126.6, 122.6, 88.7, 88.5, 18.4; MS (EI) m/z 193 (100), 192 (15), 165 (36).

2-Phenylethynyl-3-ethylpyridine (15a) : yellow oil; IR (neat/cm^{-1}) 2224; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.35 (t, J = 7.9 Hz, 3H), 2.89 (q, J = 7.9 Hz, 2H), 7.0-7.8 (m, 7H), 8.44 (dd, J = 4.8, 1.9 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 147.4, 142.6, 141.7, 135.4, 131.9, 128.8, 128.3, 122.9, 122.6, 92.4, 87.3, 26.4, 14.2; MS (EI) m/z 207 (80), 206 (100), 192 (19), 191 (20).

2-Phenylethynyl-3-ethylpyridinium picrate (15a') : yellow plates; mp 196-197 °C; Anal. Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.80; H, 3.70; N, 12.84; O, 25.66. Found: C, 57.92; H, 3.71; N, 12.75.

2-Phenylethynyl-5-ethylpyridine (15b) : yellow oil; IR (KBr/cm^{-1}) 2224; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.19 (t, J = 7.9 Hz, 3H), 2.60 (q, J = 7.9 Hz, 2H), 7.0-7.7 (m, 7H), 8.3-8.5 (m, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 149.9, 140.9, 138.7, 135.4, 132.0, 128.7, 128.3, 126.8, 122.6, 88.7, 88.5, 26.0, 15.0; MS (EI) m/z 207 (89), 192 (100), 165 (25).

2-Phenylethynyl-3-acetylpyridine (16a) : yellow oil; IR (neat/cm^{-1}) 2220, 1688; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.89 (s, 3H), 7.2-7.8 (m, 6H), 8.06 (dd, J = 8.1, 2.1 Hz, 1H), 8.74 (dd, J = 4.8, 2.1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 198.3, 152.1, 140.9, 136.9, 136.4, 131.9, 129.5, 128.5, 122.6, 121.8, 94.9, 88.1, 29.9; MS (EI) m/z 221 (100), 220 (11), 206 (39), 193 (11), 178 (39), 151 (26), 43 (13).

2-Phenylethynyl-5-acetylpyridine (16b) : colorless needles (from hexane); mp 127-128 °C; IR (KBr/cm^{-1}) 2216, 1680; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.68 (s, 3H), 7.2-7.8 (m, 6H), 8.22 (dd, J = 8.3, 2.4 Hz, 1H), 9.0-9.2 (m, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.0, 150.2, 147.2, 135.6, 132.6, 130.7, 129.5, 128.5, 126.9, 121.8, 92.6, 88.4, 26.6; MS (EI) m/z 221 (100), 206 (89), 178 (27), 151 (54), 43 (14); Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; O, 7.23. Found: C, 81.04; H, 4.95; N, 6.28.

2-Phenylethynyl-3-cyanopyridine (17a)[22] : colorless needles (from hexane); mp 103-104 °C; IR (KBr/cm^{-1}) 2220, 2200; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.2-7.8 (m, 6H), 7.97 (dd, J = 8.6, 2.1 Hz, 1H), 8.79 (dd, J = 5.5, 2.1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 152.8, 146.1, 139.7, 132.5, 130.0, 128.5, 121.9, 121.0, 96.3, 85.7; MS (EI) m/z 204 (100), 203 (24), 177 (13); Anal. Calcd. for $C_{14}H_8N$: C, 82.33; H, 3.95; N, 13.72. Found: C, 82.33; H, 3.95; N, 13.72.

2-Phenylethynyl-5-cyanopyridine (17b) : yellowish brown plates (from ethanol); mp 156-157 °C; IR (KBr/cm^{-1}) 2216, 2170; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.1-7.7 (m, 6H), 7.94 (dd, J = 9.3, 2.5 Hz, 1H), 8.84 (dd, J = 2.5, 1.1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 152.5, 146.8, 139.1, 132.3, 129.9, 128.5, 126.7, 121.3, 116.3, 108.3, 94.1, 87.7; MS (EI) m/z 204 (100), 203 (23), 177 (10); Anal. Calcd. for $C_{14}H_8N$: C, 82.33; H, 3.95; N, 13.72. Found: C, 82.71; H, 3.73; N, 13.70.

2-Phenylethynyl-3-methoxycarbonylpyridine (18a) : pale yellow oil; IR (neat/cm^{-1}) 2224, 1736, 1276, 1136; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 4.02 (s, 3H), 7.2-7.8 (m, 6H), 8.28

(dd, J = 8.1, 1.9 Hz, 1H), 8.75 (dd, J = 4.8, 1.9 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 165.7, 152.7, 151.3, 138.3, 132.5, 129.4, 128.7, 128.6, 122.6, 122.3, 94.0, 88.1, 52.7; MS (EI) m/z 237 (100), 208 (63), 206 (22), 178 (28).

2-Phenylethynyl-5-methoxycarbonylpyridine (18b) : colorless needles (from hexane); mp 140-141 °C; IR (KBr/cm^{-1}) 2220, 1724, 1290, 1136; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.2-7.8 (m, 6H), 8.29 (dd, J = 8.6, 2.1 Hz, 1H), 9.22 (dd, J = 2.1, <1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 165.5, 151.3, 147.3, 137.3, 132.4, 129.7, 128.7, 126.8, 124.8, 122.0, 92.5, 88.6, 52.6; MS (EI) m/z 237 (100), 206 (75), 151 (43); Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90; O, 13.49. Found: C, 75.78; H, 4.54; N, 5.96.

2-Hexynylpyridine (19) : colorless oil; IR (neat/cm^{-1}) 2232; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.94 (t, J = 6.7 Hz, 3H), 1.1-1.9 (m, 4H), 2.46 (t, J = 6.7 Hz, 2H), 7.19 (ddd, J = 7.6, 4.8, 1.4 Hz, 1H), 7.35 (dd, J = 7.6, 1.4, 1H), 7.62 (ddd, J = 7.6, 7.6, 1.9 Hz, 1H), 8.52 (dm, J = 4.8 Hz, 1H); MS (EI) m/z 159 (27), 158 (45), 144 (35), 130 (100), 117 (89).

2-(2-Tetrahydropyranyl)ethynylpyridine (20) : reddish orange oil; IR (neat/cm^{-1}) 1028; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.4-2.0 (m, 6H), 3.4-4.1 (m, 2H), 4.49 (s, 2H), 4.9-5.0 (m, 1H), 7.22 (ddd, J = 7.6, 5.2, 1.4 Hz, 1H), 7.43 (ddd, J = 7.6, 1.4, <1 Hz, 1H), 7.65 (ddd, J = 7.6, 7.6, 2.1 Hz, 1H), 8.57 (ddd, J = 5.2, 2.1, <1 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 149.3, 142.4, 135.6, 126.5, 122.4, 96.4, 84.9, 84.5, 61.4, 53.9, 29.7, 24.8, 18.4; MS (EI) m/z 217 (4), 133 (21), 132 (19), 130 (18), 117 (92), 116 (100), 104 (21), 90 (15), 89 (34), 85 (23).

2-Methoxycarbonylethynylpyridine (21) : colorless plates (from ethyl acetate-hexane); mp 54-55 °C; IR (KBr/cm^{-1}) 2232, 1706; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.2-7.9 (m, 3H), 8.65 (dm, J = 4.8 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 153.8, 150.5, 140.6, 136.2, 128.5, 124.5, 100.8, 84.2, 52.8; MS (EI) m/z 161 (36), 131 (19), 130 (100), 103 (15), 78 (24); Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69; O, 19.85. Found: C, 67.17; H, 4.40; N, 8.63.

2-Phenylethynylquinoline (22) : whitish yellow needles; mp 55-58 °C (lit.[23] 66-67 °C); IR (KBr/cm^{-1}) 2212; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.3-7.9 (m, 9H), 8.0-8.2 (m, 2H); ^{13}C-

NMR (90 MHz, $CDCl_3$) δ 147.9, 143.3, 135.8, 131.9, 129.7, 129.0, 128.9, 128.1, 127.2, 128.0, 126.8, 124.0, 121.9, 89.7, 89.3; MS (EI) *m/z* 229 (100), 228 (30).

1-Phenylethynylisoquinoline (23) : pale yellow granules; mp 87-92 °C (lit.[23] 97-98 °C); IR (KBr/cm^{-1}) 2216; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.2-8.0 (m, 9H), 8.3-8.7 (m, 2H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 144.3, 142.8, 135.7, 132.1, 130.4, 129.1, 128.4, 128.2, 127.8, 126.8, 122.2, 120.4, 93.9, 86.8; MS (EI) *m/z* 229 (100), 228 (54).

1-Phenylethynylisoquinolinium picrate (23') : yellow needles; mp 183-188 °C; Anal. Calcd. for $C_{23}H_{14}N_4O_7$: C, 60.27; H, 3.08; N, 12.22; O, 24.43. Found: C, 60.03; H, 3.15; N, 11.99.

2-Phenylethynylpyrimidine (24)[24] : colrless oil; IR (KBr/cm^{-1}) 2228; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.25 (t, J = 4.8 Hz, 1H), 7.3-7.5 (m, 3H), 7.71 (dd, J = 7.4, 3.8 Hz, 2H), 8.75 (d, J = 4.8 Hz, 2H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 157.3, 153.5, 132.6, 129.7, 128.4, 121.4, 119.6, 88.0, 88.0; MS (EI) *m/z* 180 (100), 127 (58).

The Preparation of *N*-Methoxypyridinum Salt 5

The preparation of the salt **5** was carried out by the similar method to the literature method.[14] The solution of pyridine *N*-oxide (**1**, 1.7 g, 17.9 mmol) in methyl iodide (3.4 ml, 53.6 mmol) was heated under reflux for 1 h. The orange precipitates were filtered, washed with ether and ethyl acetate, and dried in vacuo to give tha salt 5 (3.8 g, 16.1 mmol) in 90 % yield.

***N*-Methoxypyridinum Iodide (5)** : orange solid; ^{1}H-NMR (90 MHz, D_2O) δ 4.46 (s, 3H), 8.16 (dd, J = 7.9, 6.4 Hz, 2H), 8.56 (d, J = 7.9 Hz, 1H), 9.17 (d, J = 6.4 Hz, 2H).

Reaction of the Salt 5 with Silver Phenylacetylide

A solution of isolated salt (**5**, 356 mg, 1.5 mmol) and silver phenylacetylide (209 mg, 1mmol) in THF (5 ml) was refluxed for 1 h. The insoluble materials were filtered off and the the filtrate was concentrated, column chromatographed (Al_2O_3) to give the azatriene **6**.

1-Methoxy-8-phenyl-1(E),3(Z),5(E)-1-azaoctatriene-7-yne (6) : yellow oil; IR (neat/cm^{-1}) 2188; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.90 (d, J = 15.2 Hz, 1H), 6.04 (dd, J =

11.0, 11.0 Hz, 1H), 6.67 (dd, J = 11.0, 11.0 Hz, 1H), 7.03 (dd, J = 15.2, 11.0 Hz, 1H), 7.1-7.6 (m, 5H), 8.19 (d, J = 11.0 Hz, 1H); MS (EI) m/z 211 (48), 180 (100), 152 (37), 77 (26).

Reaction of *N*-Benzoyloxy-2-acetylpyridinum Salt and Phenylethynylmagnesium Bromide

To a solution of *N*-benzoyloxy-2-acetylpyridinum chloride (1.5 mmol) in THF (5 ml) phenylethynylmagnesium bromide[11] (1.0 mmol) was added at 0 °C and stirred for 1 h. After the reaction mixture was quenched with waterand concentrated, Et_2O (20 ml) was added and washed by 2*N* NaOH (10 ml x 3). The organic layer was dried (MgSO4), concentrated, and column chromatographed (SiO_2) to give the *N*-oxide ethynylated at acetyl group (291 mg, 0.85 mmol).

1-Phenyl-3-benzoyloxy-3-(1-oxo-2-pyridyl)-1-butyne (13) : reddish brown oil; IR (neat/cm^{-1}) 2244, 1728; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.1-7.7 (m, 10H), 8.0-8.3 (m, 3H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 163.5, 147.4, 140.3, 132.3, 131.1, 129.1, 129.1, 128.3, 127.6, 124.9, 124.5, 124.2, 121.0, 86.5, 73.7, 24.3; MS (EI) m/z 343 (3), 327 (1), 238 (3), 222 (8), 221 (8), 194 (6), 105 (100), 77 (43).

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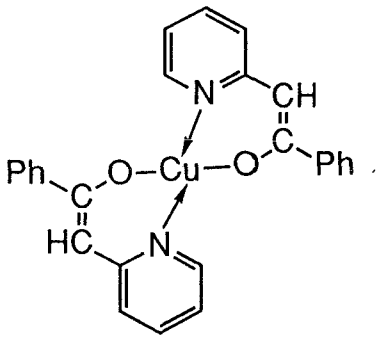
CHAPTER 2. SYNTHESIS OF FUNCTIONALIZED PHENACYLPYRIDINES

2-1. Introduction

Functionalized ethynylpyridines obtained in Chapter 1 seem to be applicable to further functionalization, transformation to bicyclic pyridines and so on. Thus in following Chapters, the functionalization reactions of ethynylpyridines were investigated utilizing the characteristics of ethynylpyridines.

In this Chapter, hydration of ethynyl group and oxidation of ring nitrogen are studied. Hydration is the representative reaction of acetylene derivatives and oxidation is that of pyridines, but different reactivities are expected in the case of ethynylpyridines.

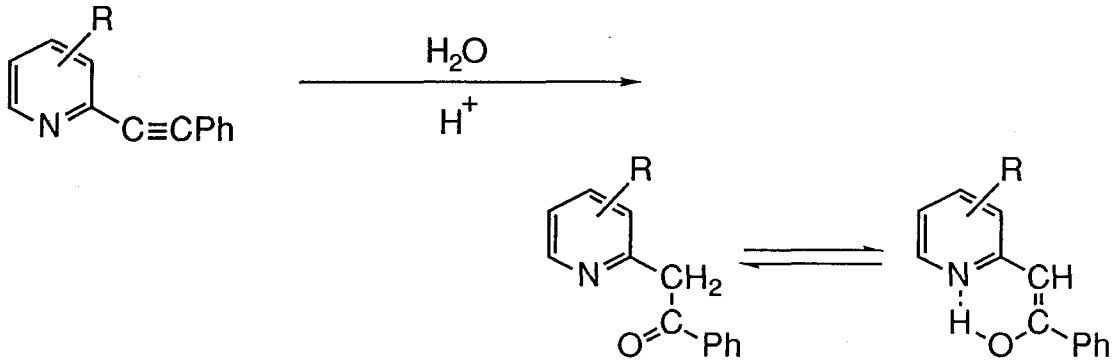
2-Phenacylpyridines are generally prepared by hydration of phenylethynylpyridines[1] or by condensation of 2-picolyl lithium and methyl benzoate.[2] It is wellknown that the enol forms of 2-phenacylpyridines are relatively as stable as keto forms[3] and that they readily form complexes metals.[4]



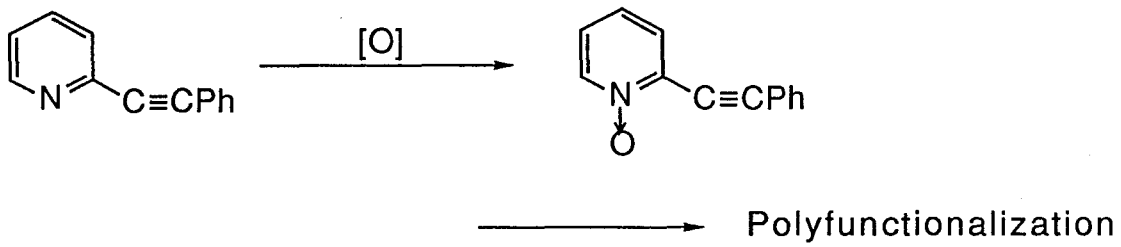
Antibacterial[5]

Based on these characters, 2-phenacylpyridines are widely utilized for antibacterials,[5] ligands and synthetic intermediates of bicyclic pyridines.[6] Although it is considered that functionalized phenacylpyridines would have more versatile reactivities, efficient synthetic methods of them are readily known and it is

strongly desired to develope the facile preparative methods. From this point of view, the hydration of phenylethynylpyridines bearing acetyl group was investigated.



On the other hand, oxidation of the ring nitrogen was also studied, since 2-ethynylpyridine *N*-oxide has not been synthesized yet.[7] If this compound is obtained, further functionalization such as bisethynylation of pyridine ring would be possible.



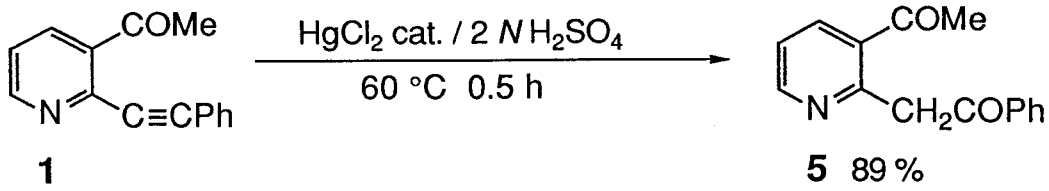
2-2. Results and Discussion

2-2-1. Hydration of Acetyl Substituted 2-Phenacylpyridines

In order to synthesize the functionalized phenacylpyridines, the hydration of acetyl substituted 2-phenylethynylpyridines was investigated.

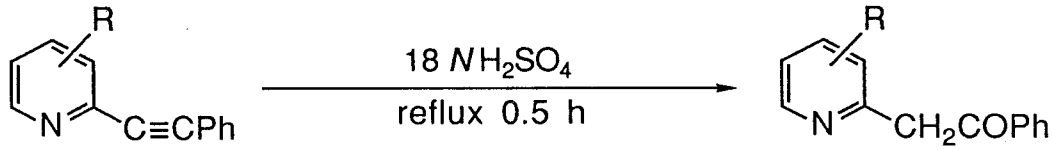
The four regio isomers **1** ~ **4** were used as substrates. When these ethynylpyridines were heated in 2 *N* sulfuric acid in the presence of mercuric chloride, which is often used in addition reactions of acetylenic compounds. 3-

Acetyl-2-phenylethynylpyridine (**1**) was transformed to 3-acetyl-2-phenacylpyridine (**5**) in 89 % yield.



1 **5** 89 %

Isomeric ethynylpyridines **2** ~ **4** were not reactive under the same conditions and recovered. While corresponding acetyl phenacylpyridines **6** ~ **8** were produced quantitatively under the conditions used for the unsubstituted 2-phenylethynylpyridine.[1] The obtained phenacylpyridines **5** ~ **8** are hitherto unknown compounds.



2 R = 4-Ac
3 5-Ac
4 6-Ac

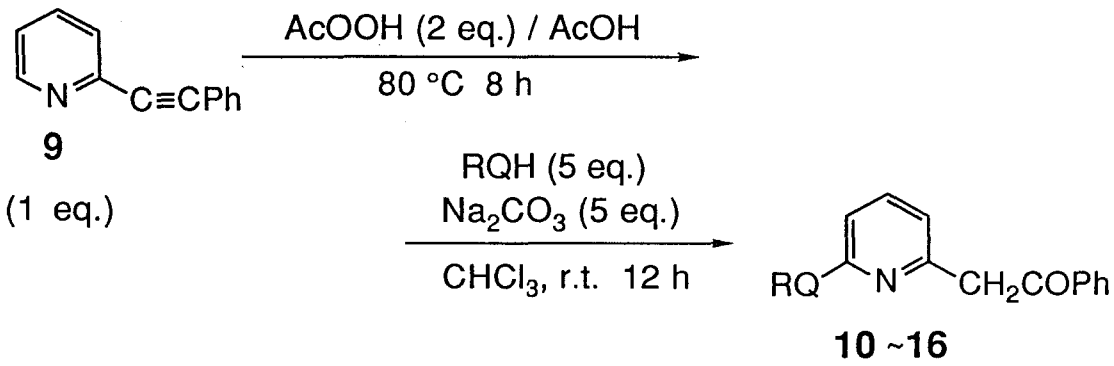
6 4-Ac 100 %
7 5-Ac 100 %
8 6-Ac 97 %

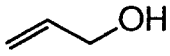
2-2-2. Studies on 2-Phenylethynylpyridine

The oxidation reaction of 2-phenylethynylpyridine was investigated. Although 4-ethynylated pyridine *N*-oxide is readily prepared by oxidation of 4-ethynylpyridine, there is no report on the synthesis of the 2-ethynylated analogue. Thus it was attemted to oxidize 2-phenylethynylpyridine **9**.

Some oxidizing agents such as *m*CPBA (*m*-chloroperbenzoic acid), sodium tungstate, and *tert*-butylhydroperoxide caused no change and the starting material was recovered.

In the case of oxidation with peracetic acid, ethynylpyridine **9** was transformed to unidentified products. However, it was found that the reaction mixture was dealt with sodium carbonate even in the presence of methanol to afford 6-methoxy-2-phenacylpyridine **10**. The present reaction proceeded in the presence of sterically hindered alcohols and corresponding 6-alkoxy-2-phenacylpyridines **11** ~ **13** were obtained in moderate yields.



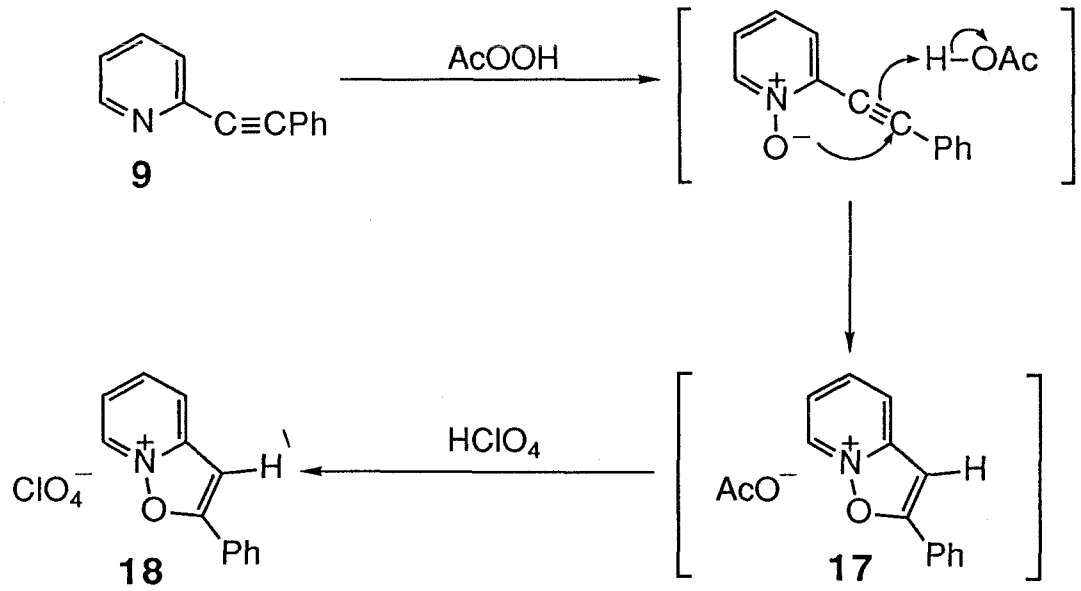
RQH	Product	Yield (%)
MeOH	**10**	62
EtOH	**11**	60
i-PrOH	**12**	49
t-BuOH	**13**	50
	**14**	15
	15	32
n-PrSH	**16**	41

The similar reaction with alcohols possessing functional group were also examined. When allyl alcohol and ethylene glycol were used, 6-substituted

derivative **14** and **15** were produced respectively. In each cases, the yields of the phenacylpyridines were decreased because of side reactions.

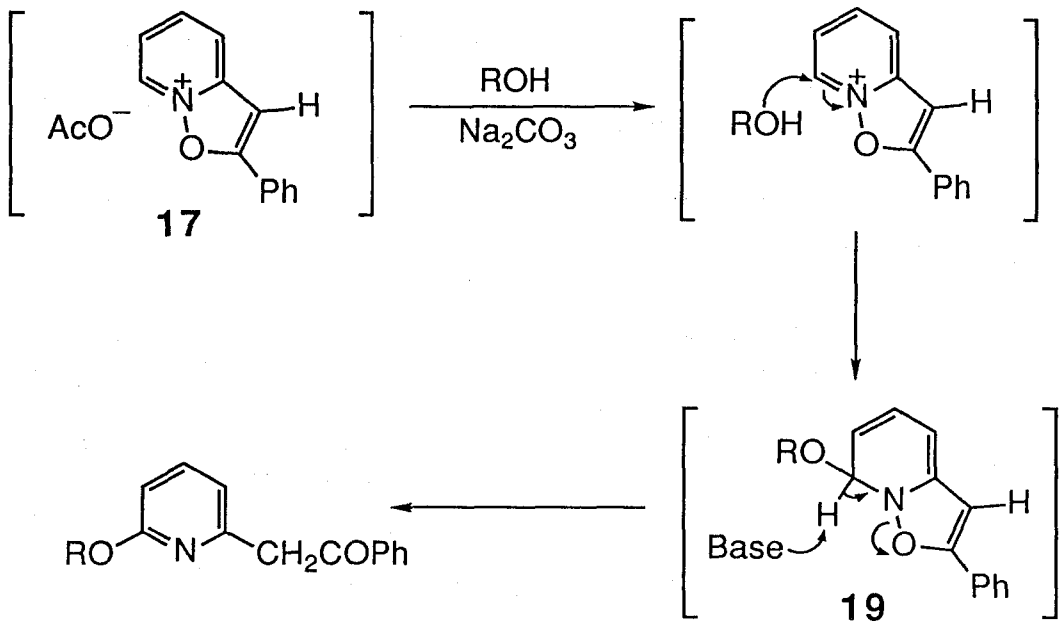
When propanethiol was employed instead of alcohol, it was also possible to introduce propylthio group into 6-position of phenacylpyridine. While, propylamine gave only a complicated mixture and desired 6-amino-2-phenacylpyridine was not detected.

In spite of attempts to identify the intermediate of this reaction after oxidation, it could not be isolated to determine its structure. Thus the present reaction was followed by ^{13}C-NMR using a mixed solvent ($CDCl_3$ / AcOH = 1/1). It was considered that isoxazolo[2,3-*a*]pyridinium salt **17**[8),9)] was formed as a plausible intermediate, since the signals similar to those of enol form of phenacylpyridine generated. Addition of perchloric acid to a reaction mixture gave 2-phenylisoxazolo[2,3-*a*]pyridinium perchlorate (**18**) as white precipitates. Hence, it was found that the salt **17** is the intermediate of this reaction.



Since the adduct **19** which was formed by the nucleophilic attack of an alcohol to the salt **17** has a good leaving group in the molecule, it was considered that the ring opening and the aromatization readily proceeded to afford 6-alkoxy-2-

phenacylpyridine. Furthermore, it was confirmed that the isolated salt **18** was transformed to phenacylpyridine **10** by treating with sodium carbonate in methanol.



As mentioned above, functionalized phenacylpyridines were easily obtained from phenylethynylpyridine utilizing hydration or oxidation reactions.

2-3. Experimental

General

Melting point was uncorrected. Mass spectra were obtained using a JEOL JMS-DX 303, and a Shimadzu GCMS-QP2000 mass spectrometer. IR spectra were recorded on a Hitachi 270-30 infrared spectrometer and NMR spectra were measured on a JEOL FT-NMR JMN FX90Q at 90 MHz with TMS as an internal standard. In this section, H^k means a proton of keto form and H^e means that of enol form.

Hydration of 3-Acetyl-2-phenylethynylpyridine (1)

A solution of ethynylpyridine **1** (110 mg, 0.5 mmol) and $HgCl_2$ (2.7 mg, 0.01 mmol) in 2 *N* H_2SO_4 (11 ml) was heated at 60 °C for 0.5 h and the reaction mixture was extracted with CH_2Cl_2 (20 ml x 4). When the reaction mixture was basified, intramolecular aldol condensation proceeded to give 5-quinolinol as described in Chapter 4. The extracts were dried ($MgSO_4$) and concentrated to afford only phenacylpyridine **5**.

3-Acetyl-2-phenacylpyridine (5) : IR (neat/cm^{-1}) 1690 (br), 1628; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.60 (s, 3H^k), 2.62 (s, 3H^e), 4.90 (s, 2H^k), 6.9-8.2 (m, 7H^k + 7H^e), 7.16 (s, 1 H^e), 8.35 (dd, J = 5.7, <1 Hz, 1H^e), 8.67 (dd, J = 6.1, <1 Hz, 1H^k), 14.1-15.0 (br, 1H^e); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 200.2, 196.9, 168.5, 157.1, 155.5, 151.6, 146.8, 140.0, 137.3, 137.0, 133.2, 130.0, 128.7, 128.4, 128.3, 126.6, 122.1, 117.1, 92.1, 47.8, 29.4, 28.6; MS (EI) m/z 239 (3), 222 (100), 105 (50).

Hydration of Other Acetyl Substituted Phenylethynylpyridines 2 ~ 4

A solution of ethynylpyridine (110 mg, 0.5 mmol) in 18 *N* H_2SO_4 (11 ml) was refluxed for 0.5 h. The reaction mixture was cooled, basified with NaOH and extracted with CH_2Cl_2 (20 ml x 4). The extracts was dried ($MgSO_4$) and concentrated to afford only phenacylpyridine.

4-Acetyl-2-phenacylpyridine (6) : reddish oil; IR (neat/cm^{-1}) 3396, 1702, 1634; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.65 (s, 3H^k), 2.73 (s, 3H^e), 4.60 (s, 2H^k), 6.18 (s, 1H^e), 7.3-8.2 (m, 7H^k + 7H^e), 8.46 (d, J = 5.7 Hz, 1H^e), 8.76 (d, J = 5.7 Hz, 1H^k); MS (EI) m/z 239 (5), 211 (10), 105 (100), 77 (73).

5-Acetyl-2-phenacylpyridine (7) : orange solid; IR (neat/cm^{-1}) 1680 (br), 1640; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.65 (s, 3H^e), 2.67 (s, 3H^k), 4.60 (s, 2H^k), 6.21 (s, 1H^e), 7.0-8.3 (m, 7H^k + 7H^e), 8.82 (dd, J = 2.4, <1 Hz, 1H^e), 9.13 (dd, J = 2.4, <1 Hz, 1H^k), 14.1-15.0 (br, 1H^e); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.4, 196.1, 194.7, 169.9, 160.9, 159.9, 149.8, 145.2, 136.6, 136.4, 136.1, 135.9, 133.6, 130.9, 130.3, 128.8, 128.6, 127.0, 126.1, 124.4, 121.3, 94.0, 48.4, 26.7, 26.2; MS (EI) m/z 239 (17), 238 (19), 211 (21), 210 (11), 105 (100), 77 (49).

6-Acetyl-2-phenacylpyridine (8) : reddish oil; IR (neat/cm^{-1}) 1700 (br), 1636; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.67 (s, 3H^k), 2.76 (s, 3H^e), 4.52 (s, 2H^k), 6.17 (s, 1H^e), 7.1-8.2 (m, 8H^k + 8H^e), 14.6 (br, 1H^e); MS (EI) *m/z* 239 (13), 211 (17), 105 (100), 77 (39).

Typical Synthetic Procedure of 6-Alkoxy-2-phenacylpyridines

A solution of ethynylpyridine **9** (180 mg, 1 mmol) and 30 % H_2O_2 (128 μl, 1.25 mmol) in acetic acid (1.8 ml) was heated at 80 °C. After 3 h, three pertions of H_2O_2 (26 μl, 0.25 mmol) were added every one hour and the whole reaction mixture was heated for further 3 h. The reaction mixture was concentrated in vacuo.

To a solution of the residue and methanol (200 μl, 5 mmol) in $CHCl_3$ (18 ml), Na_2CO_3 (0.53 g, 5 mmol) was added and stirred at room temperature for 12 h. The insoluble materials were filtered off and the filtrate was concentrated. To a residue hexane (10 ml) was added and the generated precipitates were filtered off. The filtrate was dried ($MgSO_4$) and concentrated to afford an yellow oil. It was almost the substituted phenacylpyridine, and purified through a short column (SiO_2) eluted with hexane/AcOEt to give 6-methoxy-2-phenacylpyridine **10**.

Other phenacylpyridines were obtained by similar treatments.

6-Methoxy-2-phenacylpyridine (10) : yellow oil; IR (neat/cm^{-1}) 1688, 1640; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.86 (s, 3H^k), 4.03 (s, 3H^e), 4.37 (s, 2H^k), 6.06 (s, 1H^e), 6.4-7.0 (m, 2H^k + 2H^e), 7.3-7.7 (m, 3H^k + 5H^e), 7.7-7.9 (m, 1H^k + 1H^e), 8.0-8.2 (m, 2H^k), 14.8-15.2 (br, 1H^e); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 199.2, 163.7, 161.8, 160.4, 156.0, 152.8, 139.5, 138.8, 136.8, 135.9, 132.9, 129.1, 128.8, 128.3, 128.2, 125.2, 116.4, 114.0, 108.6, 106.3, 95.7, 53.4, 53.1, 48.0; MS (EI) *m/z* 227 (4), 199 (15), 105 (100), 77 (58).

6-Ethoxy-2-phenacylpyridine (11) : yellow oil; IR (neat/cm^{-1}) 1688, 1640; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H^k), 1.47 (t, J = 7.1 Hz, 3H^e), 4.0-4.6 (m, 2H^k + 2H^e), 4.35 (s, 2H^k), 6.06 (s, 1H^e), 6.4-7.0 (m, 2H^k + 2H^e), 7.3-7.7 (m, 3H^k + 5H^e), 7.7-7.9 (m, 1H^k + 1H^e), 8.0-8.2 (m, 2H^k), 14.1 (s, 1H^e); MS (EI) *m/z* 241 (4), 213 (14), 105 (100), 77 (56).

6-Isopropoxy-2-phenacylpyridine (12) : yellow oil; IR (neat/cm^{-1}) 1688, 1642; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.25 (d, J = 6.4 Hz, 6H^k), 1.44 (d, J = 6.4 Hz, 6H^e), 4.35 (s, 2H^k), 4.9-

5.4 (m, $1H^k$ + $1H^e$), 6.06 (s, $1H^e$), 6.3-7.0 (m, $2H^k$ + $2H^e$), 7.1-7.6 (m, $3H^k$ + $5H^e$), 7.6-8.0 (m, $1H^k$ + $1H^e$), 8.0-8.2 (m, $2H^k$), 13.8-14.4 (br, $1H^e$); MS (EI) m/z 255 (2), 240 (16), 105 (100), 77 (51).

6-*tert*-Butoxy-2-phenacylpyridine (13) : yellow oil; IR (neat/cm^{-1}) 1688, 1642; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.46 (s, $9H^k$), 1.60 (s, $9H^e$), 4.32 (s, $2H^k$), 6.02 (s, $1H^e$), 6.4-6.9 (m, $2H^k$ + $2H^e$), 7.3-7.6 (m, $3H^k$ + $5H^e$), 7.6-7.9 (m, $1H^k$ + $1H^e$), 8.0-8.2 (m, $2H^k$), 13.4-14.5 (br, $1H^e$); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.9, 163.4, 162.8, 160.6, 159.9, 152.5, 138.9, 138.5, 136.6, 135.8, 132.8, 129.2, 128.8, 128.3, 128.1, 125.1, 115.6, 114.7, 111.0, 110.3, 95.5, 79.8, 79.3, 47.9, 28.9, 28.4; MS (EI) m/z 269 (0.1), 105 (100), 77 (40).

6-Allyloxy-2-phenacylpyridine (14) : yellow oil; IR (neat/cm^{-1}) 1688, 1642; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 4.37 (s, $2H^k$), 4.7-5.0 (m, $2H^k$ + $2H^e$), 5.1-5.6 (m, $2H^k$ + $2H^e$), 5.8-6.4 (m, $1H^k$ + $1H^e$), 6.06 (s, $1H^e$), 6.5-7.1 (m, $2H^k$ + $2H^e$), 7.2-7.7 (m, $3H^k$ + $5H^e$), 7.7-8.0 (m, $1H^k$ + $1H^e$), 8.0-8.3 (m, $2H^k$), 13.6-14.2 (br, $1H^e$); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.9, 163.0, 161.1, 160.4, 155.9, 152.7, 139.7, 139.0, 136.8, 135.8, 133.6, 133.0, 132.6, 129.2, 128.9, 128.4, 128.2, 125.2, 118.1, 117.3, 116.6, 114.2, 108.9, 106.7, 95.7, 67.0, 66.4, 48.1; MS (EI) m/z 253 (7), 105 (100), 77 (57).

6-Hydroxyethoxy-2-phenacylpyridine (15) : brown oil; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.8-4.0 (m, $2H^k$ + $2H^e$), 4.3-4.5 (m, $2H^k$ + $2H^e$), 4.37 (s, $2H^k$), 6.06 (s, $1H^e$), 6.6-7.0 (m, $2H^k$ + $2H^e$), 7.2-7.7 (m, $3H^k$ + $5H^e$), 7.7-7.9 (m, $1H^k$ + $1H^e$), 7.9-8.2 (m, $2H^k$), 13.8-14.3 (br, $1H^e$); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.6, 163.2, 161.1, 160.3, 155.8, 152.4, 139.6, 139.3, 136.5, 135.6, 133.0, 129.0, 128.6, 128.4, 128.1, 125.1, 116.9, 114.2, 109.0, 106.4, 95.6, 68.0, 67.6, 61.7, 60.2, 47.5; MS (EI) m/z 257 (0.3), 108 (35), 105 (100), 77 (70).

6-Propylthio-2-phenacylpyridine (16) : yellow oil; IR (neat/cm^{-1}) 1688, 1636; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.98 (t, J = 7.1 Hz, $3H^k$), 1.17 (t, J = 7.1 Hz, $3H^e$), 1.4-2.1 (m, $2H^k$ + $2H^e$), 3.06 (t, J = 7.6 Hz, $2H^k$), 3.17 (t, J = 7.6 Hz, $2H^e$), 4.43 (s, $2H^k$), 6.03 (s, $1H^e$), 6.7-7.1 (m, $2H^k$ + $2H^e$), 7.2-7.6 (m, $3H^k$ + $5H^e$), 7.7-7.9 (m, $1H^k$ + $1H^e$), 8.0-8.2 (m, $2H^k$), 14.5 (s, $1H^e$); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 196.8, 161.7, 159.1, 158.7, 156.6, 155.1, 136.7, 136.3, 135.8, 133.0, 129.2, 128.9, 128.5, 128.4, 128.2, 120.2, 119.2, 117.6, 117.1, 95.3, 48.3, 32.4, 31.9, 22.8, 22.7, 13.4, 13.4; MS (EI) m/z 105 (100), 77 (68).

2-Phenylisoxazolo[2,3-*a*]pyridinium perchlorate (18) : colorless needles; mp 200-201 °C; IR (KBr/cm^{-1}) 1094; ^{1}H-NMR (90 MHz, d_6-DMSO) δ 7.6-7.8 (m, 3H), 7.8-8.2 (m, 4H), 8.4-8.6 (m, 2H), 9.89 (d, J = 7.1 Hz, 1H); ^{13}C-NMR (90 MHz, d_6-DMSO) δ 164.0, 145.5, 139.7, 133.2, 131.1, 129.9, 126.8, 123.5, 121.6, 121.1, 98.9; MS (EI) m/z 105 (100), 77 (81).

2-4. Refferences

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2) J. F. Wolfe, D. E. Portlock, and D. J. Feuerbach, *J. Org. Chem.*, 1974, **39**, 2006.

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8) R. H. Good and G. Jones, *J. Chem. Soc. (C)*, **1971**, 1196.

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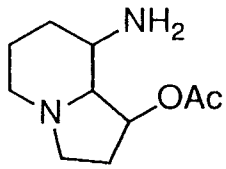
CHAPTER 3. SYNTHESIS OF [*a*]-FUSED PYRIDINES

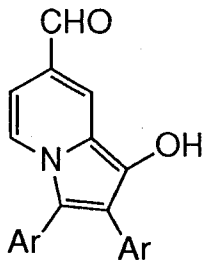
3-1. Introduction

Bicyclic pyridines are of great importance since this skeleton is often found in natural alkaloids, in biologically active substances such as medicines and agrochemicals, as well as in various functional materials such as dyes, chelating agents and so on. Hence, it is one of important subjects to develope new reagents or new methods for preparation of novel or suitably functionalized pyrido compounds. In this Chapter and next Chapter, syntheses of [*a*]-fused pyridines and [*b*]-fused pyridines from ethynylpyridines are described.

Indolizines are representative compounds among [*a*]-fused pyridines and thus, indolizine skeleton was focused on by my attention and investigated. Apart from interests in their syntheses and properties, some of the works on indolizines have been concerned with the search for drugs, for dyestuffs, and for light-screening agents used in photographic emulsions or synthetic intermediates of cyclazine derivatives.[1] Furthermore, the skeletons of their perhydro derivatives are often found in the indolizidine alkaloids. Althogh indolizine derivatives show various functions as mentioned above, there are few preparative methods of indolizine skeletons.



slaframine[2]
(alkaloid)



oxoindolizine dye[3]

Since ethynylpyridines have an ethynyl group and the nucleophilic ring nitrogen, they are expected to be synthetic intermediates of [*a*]-fused bicyclic

compounds. However, few synthetic methods of indolizines from ethynylpyridines are known.[4)]

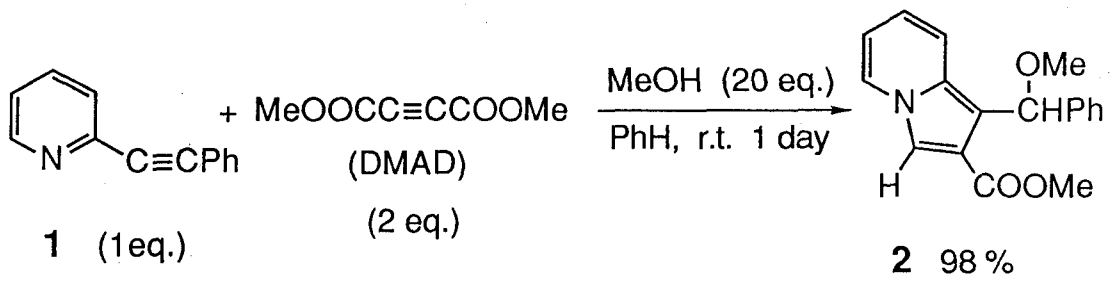
In this Chapter, the cycloaddition of ethynylpyridines and dimethyl acetylenedicarboxylate (DMAD) producing the indolizine derivatives was studied. The structures of indolizines were determined by spectral and analytical data and the plausible reaction path of this reaction was also discussed. Furthermore, an oligomer of the indolizine derivative was synthesized and its pH sensitive behavior was clarified.

3-2. Results and Discussion

3-2-1. Studies on Cycloaddition of Ethynylpyridines

a) Typical Reaction and Determination of the Structure

2-Phenylethynylpyridine (**1**) readily reacted with dimethyl acetylenedicarboxylate (DMAD) in the presence of methanol to give 1-(α-methoxybenzyl)-2-methoxycarbonylindolizine (**2**) quantitatively. Although Acheson and Bridson

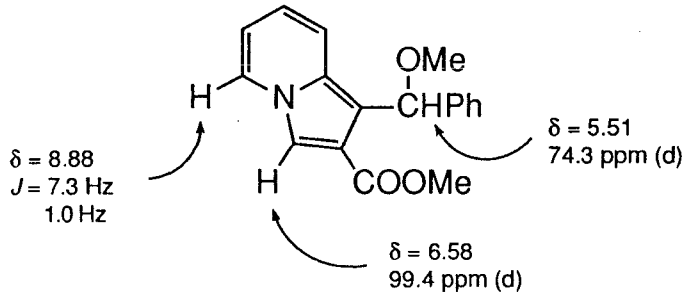


1 (1eq.)

2 98 %

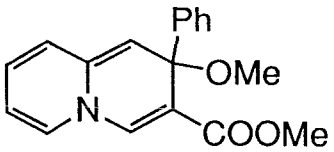
reported the similar reaction in alcohol, they isolated only unidentified products.[5)]

The structure of **2** was determined by spectral and analytical data as follows. It was readily confirmed that the indolizine **2** is the demethoxycarbonylated product from the adduct of ethynylpyridine **1**, DMAD and methanol by mass and ^{13}C-NMR spectra. Since it is known that quinolizine derivative is obtained from pyridine and DMAD,[6)] quinolizine **3** is an alternative structure for the present product. However, this possibility was easily excluded by observation of a doublet signal of sp^3 carbon at δ 74.3 ppm ($J_{C\text{-}H}$ = 143.6 Hz) in the ^{13}C-NMR spectrum.



IR (neat / cm^{-1})
1750 (C=O)

MS
295 (M$^+$, 37 %)



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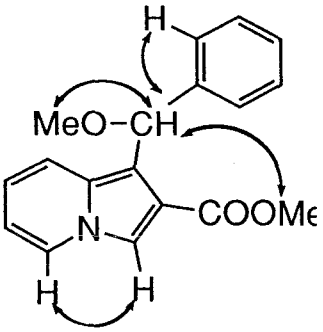
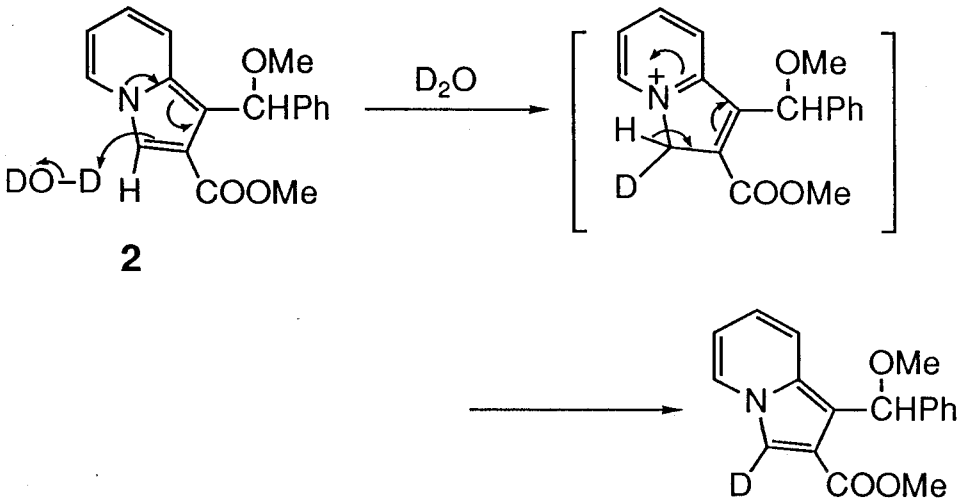


Correlations of NOE

The position of the methoxycarbonyl group was determined by the measurement of ^{1}H-^{1}H 2D NMR nuclear Overhauser enhancements (NOEs). The structure was well supported by the correlations of the observed NOEs; namely the NOEs between the proton at benzyl position and two methoxy groups and that between two protons at 3- and 5-positions were observed.

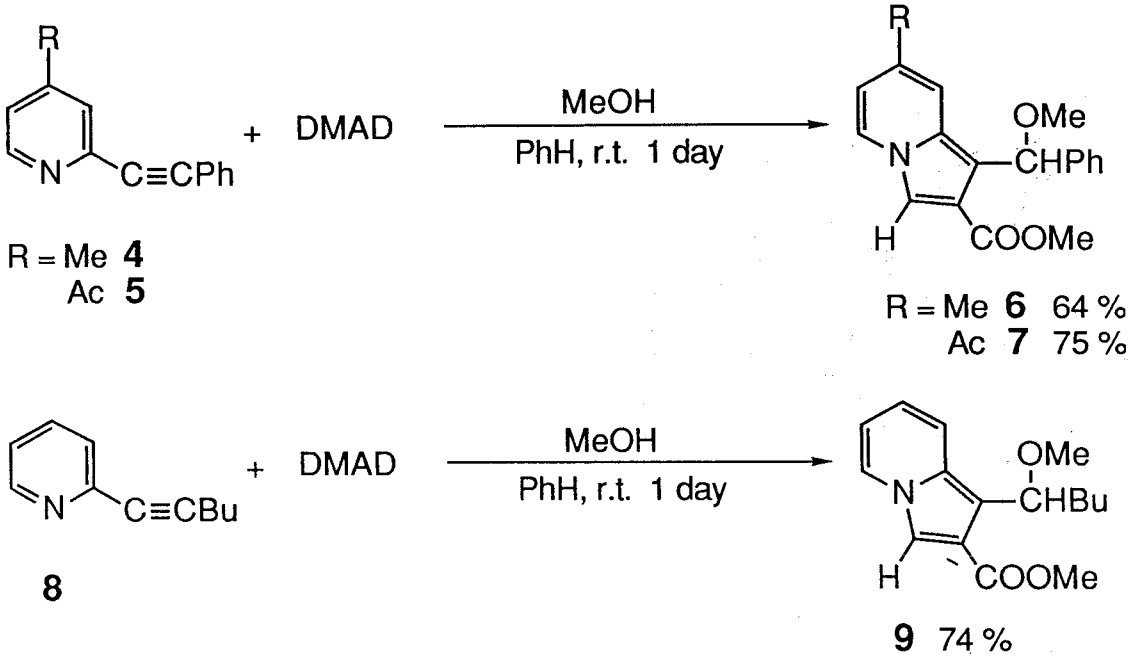
While it is wellknown that 1- and 3-positions of indolizine derivatives are nucleophlic positions and proton exchange at these positions easily proceeds. When the indolizine **2** was stood in the presence of D_2O in $CDCl_3$, the signal of the proton at 3-position (δ 6.53) gradually decreased and completely disappeared after 3 days.[1)7)] This result indirectly supported that the methoxycarbonyl group was substituted at 2-position.



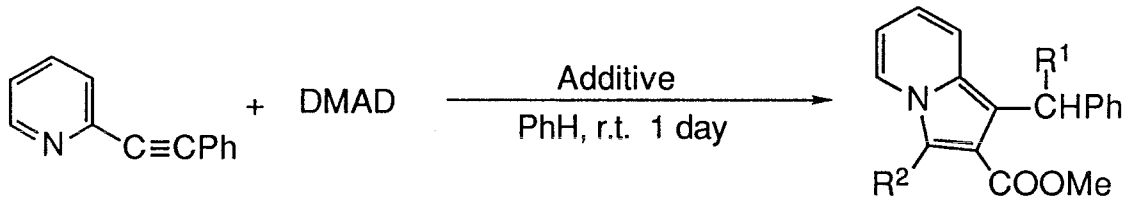
b) Reactions with Other Substrates

Other dipolarophiles such as methyl acetylenemonocarboxylate, dimethyl maleate, and *N*-phenylmaleimide were examined. Unfortunately, these are not reactive under the similar conditions and ethynylpyridine **1** was recovered.

The present method was applicable to substituted ethynylpyridines. The 4-substituted ethynylpyridines **4** and **5** gave the corresponding 7-substituted indolizine derivatives **6** and **7** in moderate yields, respectively. As the acetyl group of **5** was not changed at all through the reaction, it is possible to synthesize polyfunctionalized indolizines. 2-Hexynylpyridine **8** also reacted with DMAD to give the corresponding indolizine **9** in 74 % yield, showing aliphatic acetylenic derivative can be used as a substrate.



In the absence of alcohol, the reaction of the pyridine **1** with DMAD in benzene or tetrahydrofuran became much complicated. Thus several alcohols were studied as a proton source which seems to be essential for this reaction.



Additive	Indolizine			Yield (%)[a)]
		R^1	R^2	
MeOH	**2**	MeO-	H	98
EtOH	**10**	EtO-	H	80
i-PrOH	**11**	*i*-PrO-	H	34
t-BuOH	**12**	*t*-BuO-	COOMe	77
$(MeOOC)_2CH_2$	**13**	$(MeOOC)_2CH$-	COOMe	63

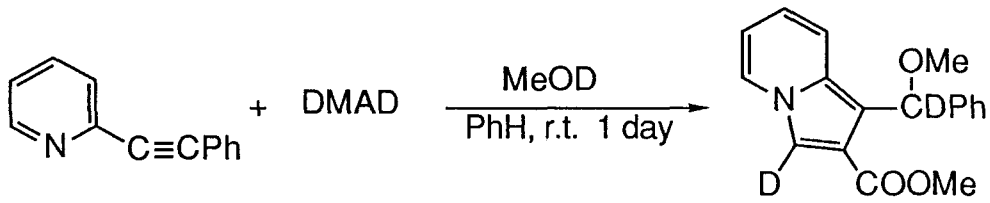
a) Determined by ^{1}H-NMR

With ethanol and isopropanol, the reaction proceeded similarly and formed the products **10** and **11**, respectively. In contrast, demethoxycarbonylation at 3-position did not occur in the case of *tert*-butanol and bis(methoxycarbonyl) derivative **12** was obtained.

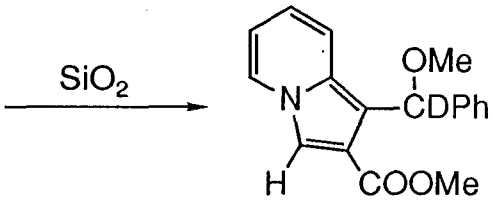
Furthermore, it is noteworthy that the reaction in the presence of dimethyl malonate instead of an alcohol resulted in the carbon-carbon bond formation at benzyl position and gave the indolizine **13**.

c) Studies on Reaction Path

When MeOD was used in place of MeOH, the product **14** deuterated at benzyl position and 3-position of the indolizine skeleton was obtained in 98 % yield (monodeuterated indolizine **15** was isolated through the column chromatography on silica gel because of ready H-D exchange at 3-position : see referrence 1 and 7). This result shows that these two protons come from the alcohol.

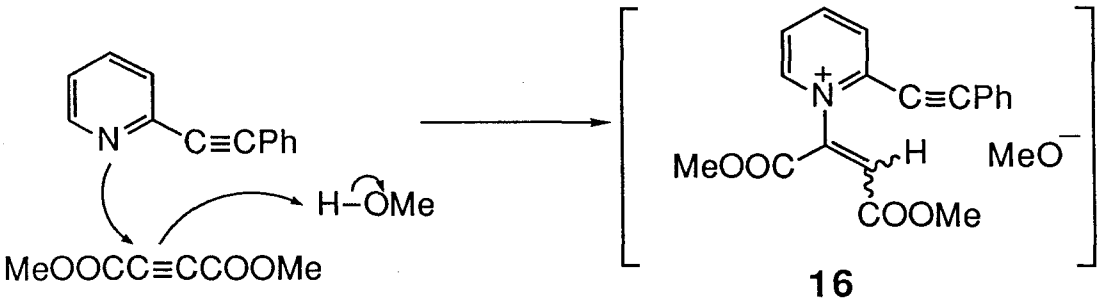


14

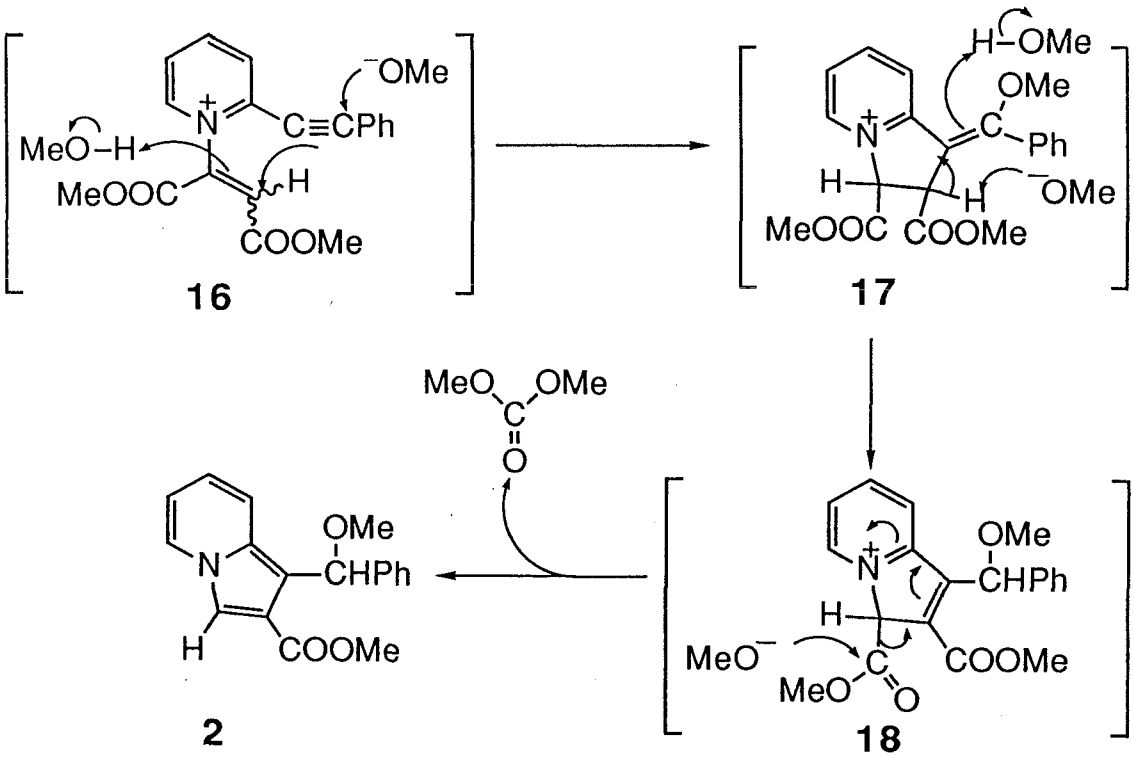


15

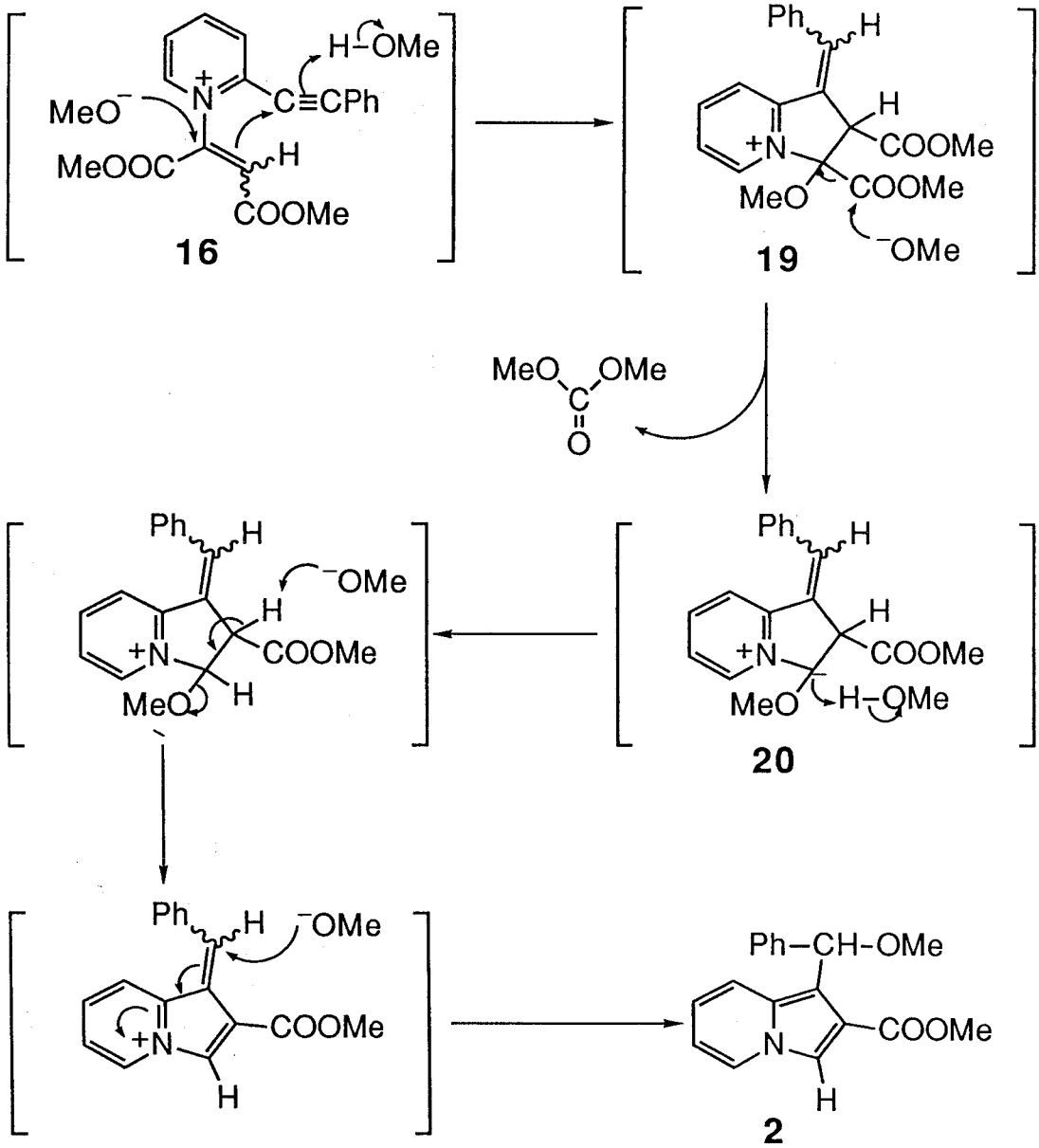
The plausible reaction path is assumed as follows. After the nucleophilic attack of the ring nitrogen to the sp carbon of DMAD, successive protonation of the adduct gave the pyridinium intermediate **16**.



The ring closure of **16** leads to indolizine skeleton, where, two routes are mainly considered. Namely, the attack of a counter anion, methoxide anion, occurs at the ethynylgroup or at the vinyl group.



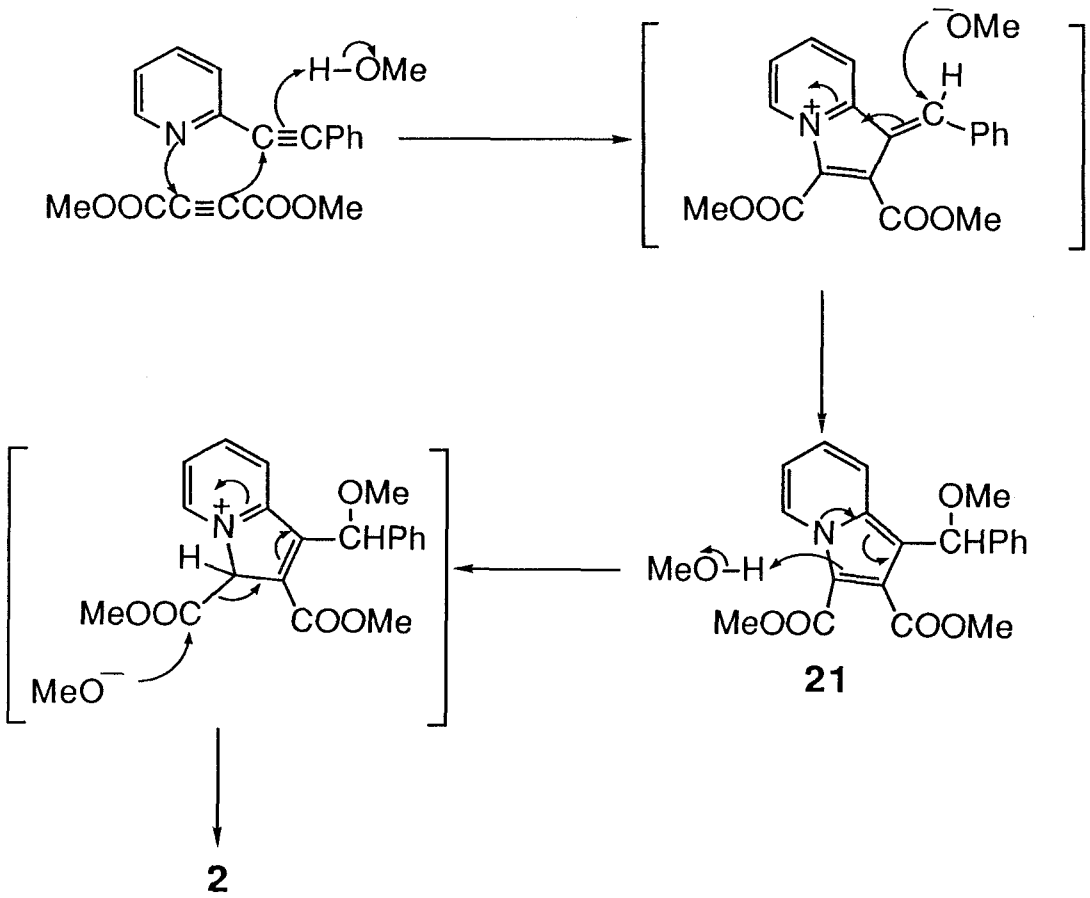
In the case of the attack of the methoxide to an ethynyl group, the intermediate **17** is produced and rearrangement of proton at 2-position undergoes to give **18**. Demethoxycarbonylation at 3-position proceeds to afford indolizine derivative **2** as shown below.



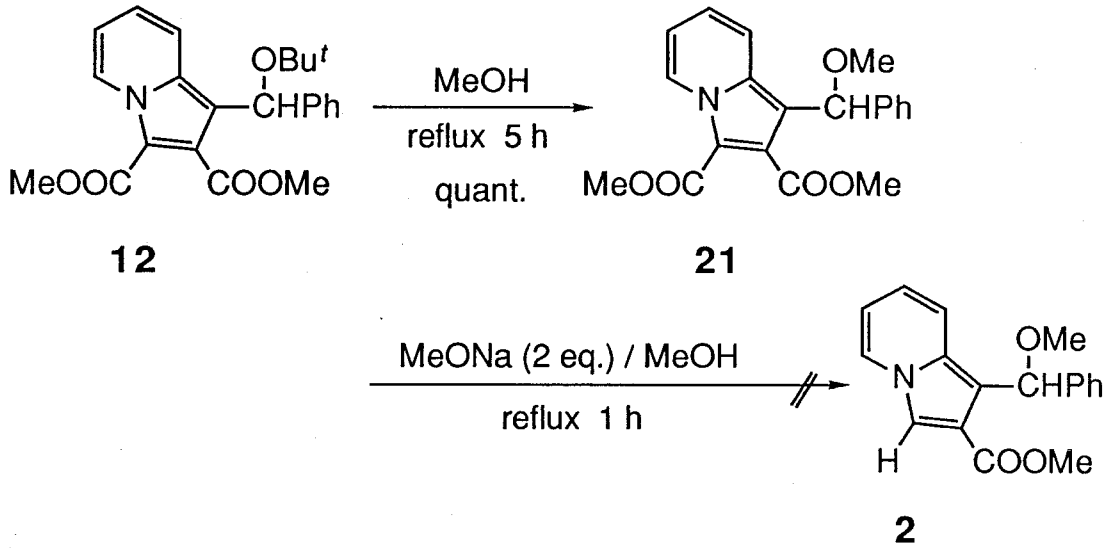
An alternative path for demethoxycarbonylation is conceivable. When the methoxide anion attacks to the vinyl group, the intermediate **19** is produced and the demethoxycarbonylation at 3-position proceeds to give pyridinium yilide **20**. The successive aromatization affords the indolizine derivative **2**.

In each case, elimination of methoxycarbonyl group is considered to be caused by attack of methoxide anion, the counter anion of the intermediate. It is consistent with the detection of dimethyl carbonate equimolar to indolizine **2**. When the sterically hindered proton sources, *tert*-butanol and dimethyl malonate, are used, they are thought unable to attack the methoxycarbonyl group.

On the other hand, there is a route containing a direct ring closure as another path.



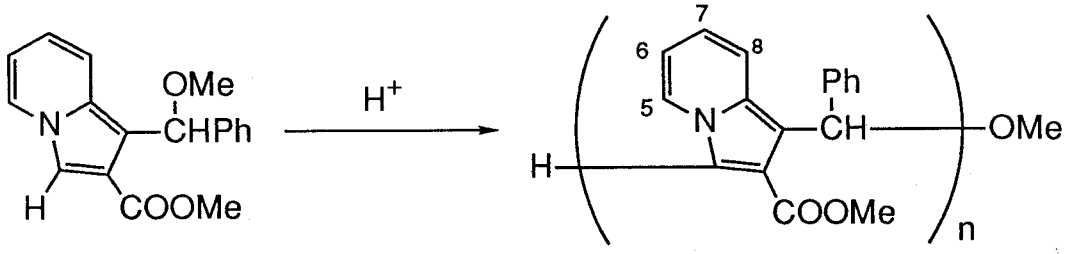
However, this route is easily excluded by the results of the experiment using **12** as follows. On heating the 2,3-bis(methoxycarbonyl) derivative **12** in methanol, substitution at benzyl position occurred to give the analogue **21**. Generation of methoxide anion in the reaction of phenanthridine and DMAD in methanol is reported,[7] but further treatment of **21** with sodium methoxide (2 equiv.) in methanol caused no change such as demethoxycarbonylation at 3-position leading to **2**.



3-2-2. Studies on the Oligomer of Indolizine Derivative

a) Oligomerization of Monomethoxycarbonylindolizine

While bis(methoxycarbonyl) indolizine derivatives were comparatively stable against acid, in contrast, monomethoxycarbonyl derivatives were unstable toward acids and readily oligomerized. For example, indolizine **2** was transformed to bluish green oligomer **22** upon acidic treatment or strage in chloroform. Oligomers or polymers of indolizine derivatives are hitherto unknown and there has been only one example of polymer-supported indolizine dye.[8] Hence, the present oligomer **22** is interesting in points of the chemical and physical properties.



2 22

The indolizine **2** (50 mg) was readily oligomerized by stirring in commercially available chloroform (15 ml) at room temperature to give the oligomer **22** quantitatively. The oligomer **22** was easily soluble in chloroform, dichloromethane, tetrahydrofuran and 1,4-dioxane. The reaction was monitored by thin layer chromatography (TLC) developed with hexane/AcOEt (50/50) and was stopped when the original spot showed no change. After stirring for 0.5 h, the reaction mixture turned to bluish green, and the reaction completed after 1 day. The rate of oligomerization was influenced by the amount of the solvent. When one third amount of chloroform (5 ml) was used, 3 days were required to complete the reaction.

Under basic conditions, this reaction was depressed and 50 % of the starting material was recovered even after 5 days. Thus the oligomerization was thought to be catalyzed by hydrochloric acid which was contained in chloroform. The oligomer was also obtained when **2** was stirred in tetrahydrofuran containing hydrochloric acid (equimolar to **2**) or silica gel, or in acetic acid. In these cases, longer reaction times than the case with chloroform were needed. Thus chloroform was found to be the most suitable solvent containing the catalyst for the present reaction.

b) Structual Determination of Oligomer

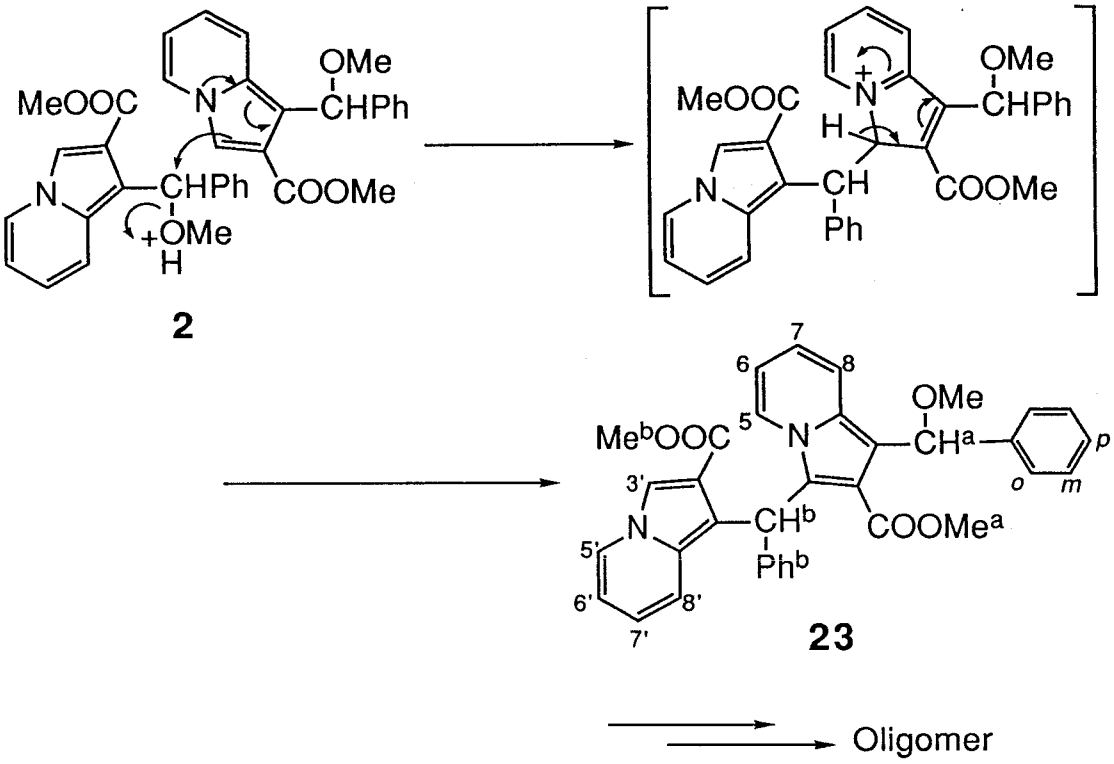
The weight-average molecular weight of the oligomer **22** was about 1500 using polystyrene as a standard. No cleavage in the methoxycarbonyl group at 2-position was observed by IR spectrum. When the reaction was monitored by ^{1}H-NMR, the generation of methanol (δ 3.48) eliminated during the oligomerization was observed.

From these results along with other spectral data, the structure of the oligomer was determined as **22**. This structure was supported by the comparison with the dimer **23** or the trimer of **2** isolated in the earlier stage of the reaction.

The structures of the dimer and the trimer were established by spectral and analytical data. It was confirmed by the mass spectrum that each of these was the bimolecularly or trimolecularly condensed compound accompanied by elimination of one or two molecules of methanol. The ^{1}H-NMR spectra were satisfactorily assigned to the structures and one of the features of the spectra is the signals of the inner protons (H-5, 6, 8', Ph^{b}, $COOMe^{b}$) of **23** were observed in higher fields than the signals of the outer protons or the corresponding signals of monomer **2**. This observation could be explained by that the indolizine rings are torsionally restrained and the protons at the inside positions are located on the other indolizine ring. The dimer **23** was found to be the mixture of isomers (73/27) by ^{1}H-NMR and the coalesced spectrum was not obtained on a measurement at 70 °C. ^{13}C-NMR spectrum of the dimer was too complicate to be assigned, but the six signals of methoxy carbons were confirmed (at δ 51.38, 51.44, 51.50, 51.61(COOMe x 4), 56.28, 56.51 (OMe x 2)).

c) The Plausible Path of Oligomerization

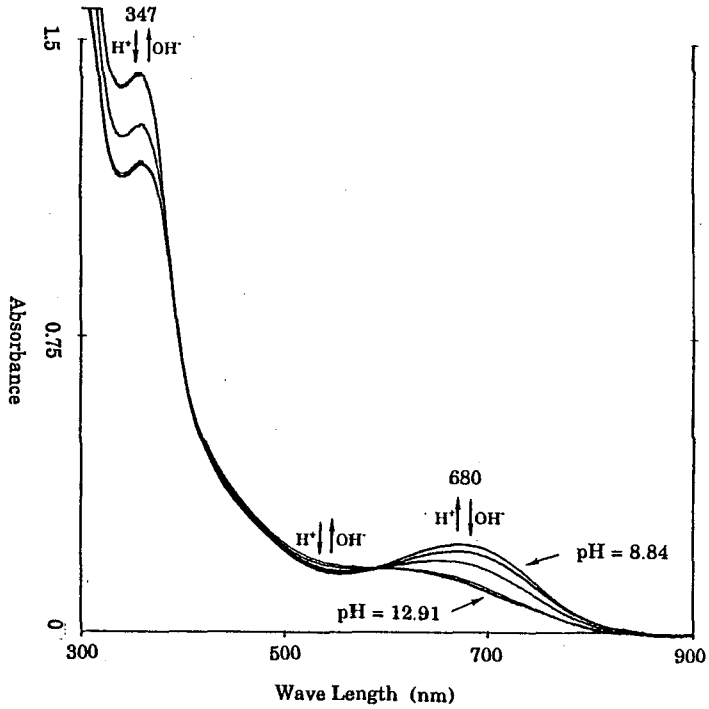
From these results, the oligomerization was thought to proceed as follows. Indolizine derivatives are known to have nucleophilicity at 1- and 3-positions.[1)7)] In this case, the indolizine **2** activated by protonation was considered to be attacked by the carbon at 3-position of **2** to produce the dimer **23** via the successive aromatization. Repetition of this condensation reaction will reasonably lead to the oligomer **22** under acidic conditions. This path is supported by the generation of methanol during the oligomerization.



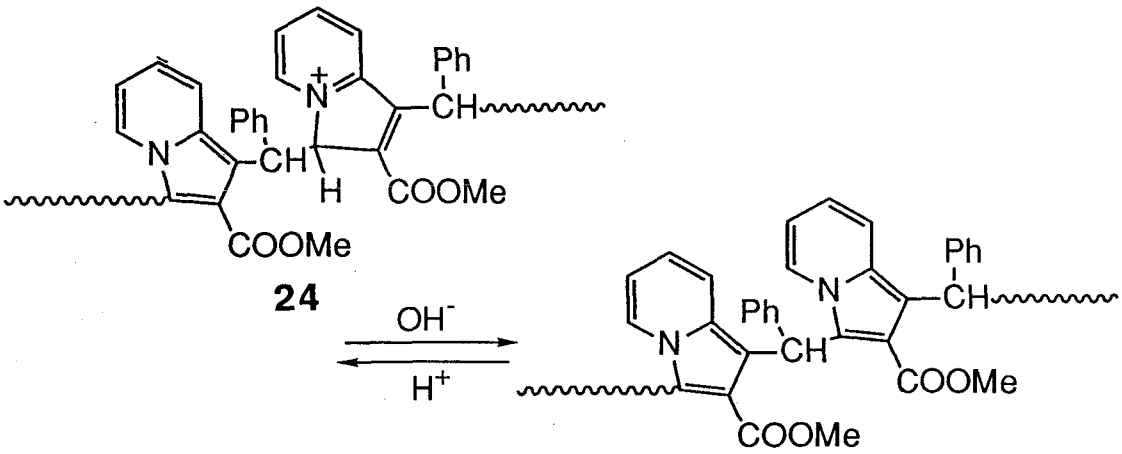
d) pH Sensitive Behavior of Oligomer 22

Under basic conditions, the color of the oligomer **22** turned to yellowish brown from bluish green. This transformation was performed with bubbling ammonia gas to a solution of **22** in tetrahydrofuran for 5 min. To change the color, sodium hydroxide was also available instead of ammonia. The solution was concentrated to give the hygroscopic yellowish brown solid. The compound possessed ester groups whose absorption was observed at 1730 cm^{-1} in the IR spectrum.

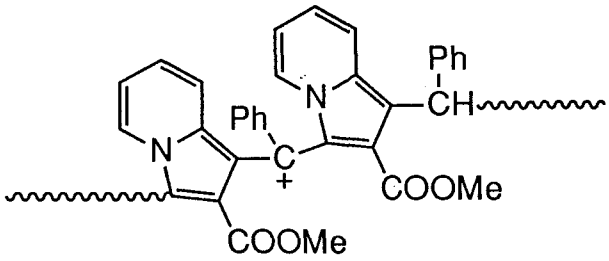
The change of color was clearly observed on the UV-Vis. spectra, namely the absorbance decreased at 680 nm and increased at 347 nm. On the other hand, the color returned to bluish green under acidic conditions. This change of color was reversible and its pK_{obs} was 11.1.



Although the reasons of the change of color have not been clarified yet, as one of possibilities it is considered that the unit **24** exists in the oligomer and changes depending on pH.



The structure of **22** has resemblance to diphenyl or triphenylmethane type dyes.[9] Since these type of dyes are almost cationic, there is another possibility of existence of the unit **25** in the oligomer.



25

There seems to be possibility to apply the present pH sensitive material to a functional dye by modification of monomeric indolizine derivatives.

3-3. Experimental

General

Melting points are uncorrected. Mass spectra were obtained using a Shimadzu GCMS-QP2000 mass spectrometer and high resolution mass spectrum (HRMS) was recorded with a JEOL JMS-DX303 mass spectrometer. IR spectra were recorded on a Hitachi 270-30 infrared spectrometer and ^{1}H-NMR spectra were measured on JEOL FT-NMR JMN FX90Q at 90 MHz, JEOL FT-NMR GSX at 270 MHz or JEOL JMN-GSX-400 at 400 MHz with TMS as an internal standard. Elemental analyses were performed on Yanagimoto CHN-Corder Mt-2.

The molecular weight distribution of the oligomer **16** was determined by gel permeation chromatography (GPC) using Toyo Soda HLC CP8000 with Cosmosil 5GPC-100 and 5GPC-300 (Toyo Soda), and UV detector operating at 254 nm with THF as an eluent.

Typical Procedure of Synthesis of Indolizines :

To a benzene solution (10 ml) of 2-phenylethynylpyridine (179 mg, 1 mmol), MeOH (0.81 ml, 20 mmol) and DMAD (246 μl, 2 mmol) were added and stirred at room temperature for one day. The mixture was concentrated and chromatographed (SiO_2 - hexane/AcOEt = 95/5) to give 1-(α-methoxybenzyl)-2-methoxycarbonylindolizine as a pale yellow oil in 85 % yield.

Other indolizine derivatives were obtained from the corresponding hydrogen source and ethynylpyridines by the similar procedure.

1-(α-Methoxybenzyl)-2-methoxycarbonylindolizine (2) : pale yellow oil; IR (neat/cm^{-1}) 1750, 1198, 1096; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.20 (s, 3H), 3.75 (s, 3H), 5.37 (s, 1H), 6.53 (s, 1H), 6.4-6.9 (m, 2H), 7.2-7.7 (m, 6H), 8.37 (d, J = 7.1 Hz, 1H); (400 MHz, C_6D_6) δ 2.97 (s, 3H), 3.15 (s, 3H), 5.51 (s, 1H), 6.26 (ddd, J = 7.3, 6.8, 1.0 Hz, 1H), 6.44 (ddd, J = 8.8, 6.8, 1.0 Hz, 1H), 6.58 (s, 1H), 7.13 (dd, J = 8.8, 1.0 Hz, 1H), 7.25 (dd, J = 8.8, 1.5 Hz, 1H), 7.38 (dd, J = 8.3, 1.5 Hz, 1H), 7.81 (dd, J = 8.8, 8.3 Hz, 1H), 8.80 (dd, J = 7.3, 1.0 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 169.6, 135.5, 133.4, 132.1, 129.4, 128.3, 126.8, 125.0, 118.5, 118.1, 113.4, 110.5, 99.4, 74.3, 56.2, 52.1; MS (FAB) m/z 295 (37), 264 (23), 236 (100), 220 (14), 204 (14); Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74; O, 16.25. Found: C, 72.87; H, 5.87; N, 4.69.

1-(α-Methoxybenzyl)-2-methoxycarbonyl-7-methylindolizine (6) : colorless plates; mp 100.5-101.5 °C; IR (neat/cm^{-1}) 1746; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.29 (d, J = 0.8 Hz, 3H), 3.19 (s, 3H), 3.76 (s, 3H), 5.35 (s, 1H), 6.38 (dd, J = 7.6, 1.9 Hz, 1H), 6.40 (s, 1H), 7.13 (brs, 1H), 7.3-8.2 (m, 5H), 8.29 (d, J = 7.6 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 169.7, 136.8, 134.5, 132.6, 133.0, 128.8, 128.4, 127.1, 125.7, 117.3, 114.0, 113.4, 98.9, 75.3, 56.3, 51.6, 20.7; MS (FAB) m/z 309 (41), 278 (25), 250 (100); Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53; O, 15.51. Found: C, 73.49; H, 6.34; N, 4.31.

1-(α-Methoxybenzyl)-2-methoxycarbonyl-7-acetylindolizine (7) : yellow oil; IR (neat/cm^{-1}) 1752, 1674; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.24 (s, 3H), 3.77 (s, 3H), 5.38 (s, 1H), 6.84 (s, 1H), 7.18 (dd, J = 7.6, 1.9 Hz, 1H), 7.3-7.6 (m, 5H), 8.05-8.15 (m, 1H), 8.39 (dd, J = 7.6, 1.0 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 195.5, 169.2, 134.6,

133.6, 131.8, 129.3, 128.5, 127.3, 127.2, 124.6, 121.6, 117.1, 108.3, 105.2, 74.2, 56.7, 52.4, 25.5; MS (EI) *m/z* 337 (14), 307 (12), 278 (100), 263 (13), 248 (36); Fluorescence ($CHCl_3$/nm) λ_{em} = 515 (λ_{ex} = 350), λ_{em} = 470, 520 (λ_{ex} = 250).

1-(α-Ethoxybenzyl)-2-methoxycarbonylindolizine (10) : pale yellow oil; IR (neat/cm^{-1}) 1750, 1096; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.08 (dd, *J* = 7.0, 7.0 Hz, 3H), 3.27 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.43 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.74 (s, 3H), 5.48 (s, 1H), 6.52 (s, 1H), 6.4-6.9 (m, 2H), 7.3-7.7 (m, 6H), 8.46 (dd, *J* = 7.1, 1.0 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 169.9, 135.7, 133.5, 131.9, 129.4, 128.3, 126.8, 125.3, 118.6, 118.2, 114.1, 110.4, 99.4, 72.7, 64.2, 52.2, 14.7; MS (EI) *m/z* 309 (11), 250 (100), 222 (34), 204 (19); Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53; O, 15.51. Found: C, 73.96; H, 6.25; N, 4.54.

1-(α-Isopropoxybenzyl)-2-methoxycarbonylindolizine (11) : whitish yellow plates; mp 91-92 °C; IR (neat/cm^{-1}) 1730, 1268; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.1 Hz, 6H), 3.37 (hept, *J* = 6.1 Hz, 1H), 3.75 (s, 3H), 5.58 (s, 1H), 6.51 (s, 1H), 6.4-6.9 (m, 2H), 7.3-7.8 (m, 6H), 8.50 (dd, *J* = 7.1, 1.0 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 170.4, 135.9, 133.6, 131.8, 129.5, 128.4, 126.9, 125.7, 118.6, 118.3, 114.6, 110.4, 99.4, 70.5, 69.6, 52.3, 22.1, 21.4; MS (EI) *m/z* 323 (23), 264 (91), 222 (100).

1-(α-*tert*-Butoxybenzyl)-2,3-dimethoxycarbonylindolizine (12) : pale yellow plates; mp 118-119 °C; IR (neat/cm^{-1}) 1738, 1694; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.22 (s, 9H), 3.87 (s, 3H), 3.95 (s, 3H), 5.94 (s, 1H), 6.80 (ddd, *J* = 8.6, 6.7, 1.9 Hz, 1H), 6.98 (ddd, *J* = 8.6, 8.6, 1.9Hz, 1H), 7.1-7.6 (m, 5H), 7.73 (ddd, *J* = 8.6, 1.9, 1.2 Hz, 1H), 9.35 (ddd, *J* = 6.7, 1.9, 1.2 Hz, 1H),; ^{13}C-NMR (90 MHz, $CDCl_3$) δ 166.9, 160.5, 144.0, 133.8, 127.8, 126.8, 126.4, 126.1, 125.3, 121.3, 119.4, 117.8, 113.8, 109.7, 74.9, 68.9, 51.9, 51.0, 27.9; MS (EI) *m/z* 395 (44), 338 (27), 322 (100), 306 (86), 274 (10), 262 (25), 230 (53); Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54; O, 20.23. Found: C, 69.77; H, 6.36; N, 3.54.

1-(α-(Dimethoxycarbonylmethyl)benzyl)-2,3-dimethoxycarbonylindolizine (13) : pale yellow plates; mp 158-59 °C; IR (KBr/cm^{-1}) 1738, 1694; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.61 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.66 (d, *J* = 12.2 Hz, 1H), 5.21 (d, *J* = 12.2 Hz, 1H), 6.7-7.8 (m, 8H), 9.33 (ddd, *J* = 7.1, 1.2, 1.2 Hz, 1H),; ^{13}C-NMR (90 MHz, $CDCl_3$) δ 167.9, 167.6, 167.0, 160.3, 139.9, 134.3, 128.1, 127.3, 126.8, 126.5, 126.2, 122.4,

117.5, 113.9, 112.9, 110.7, 55.0, 55.0, 52.3, 52.0, 51.1, 41.1; MS (EI) *m/z* 453 (18), 322 (100).

1-(α-Methoxybenzyl)-2,3-dimethoxycarbonylindolizine (21) : pale yellow plates; mp 107-108 °C; IR (KBr/cm^{-1}) 1742, 1704; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 5.58 (s, 1H), 6.8-7.6 (m, 8H), 9.38 (dm, J = 6.9 Hz, 1H),; ^{13}C-NMR (90 MHz, $CDCl_3$) δ 166.6, 160.4, 141.2, 133.8, 127.9, 127.2, 127.0, 127.0, 126.2, 122.2, 118.7, 114.0, 113.6, 109.9, 78.1, 56.6, 52.1, 51.1; MS (EI) *m/z* 353 (35), 322 (100), 306 (38), 276 (26), 204 (17); Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96; O, 22.64. Found: C, 67.56; H, 5.32; N, 3.91.

Oligomerization of indolizines 2

A solution of indolizine **2** (50 mg, 0.7 mmol) in chloroform (15 ml) was stirred at room temperature for 1 day. The solution was concentrated in vacuo and the residual solid was washed with hexane to give the oligomer **22** quantitatively.

Bluish green solid; mp >300 °C; IR (KBr/cm^{-1}) 1740; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 2.8-3.5 (br, 3H), 5.4-5.7 (br, 1H), 5.8-6.6 (br, 3H), 6.7-7.6 (br, 5H), 7.6-8.1 (br, 1H). The oligomer **22** was not burnt completely even when excessive oxygen was used and satisfactory analytical data were not obtained.

Oligomerization under Basic Conditions

Chloroform was washed with saturated $NaHCO_3$ aq. (30 ml x 2) prior to the reaction. A solution of **2** in base-washed chloroform (15 ml) was stirred in the presence of $NaHCO_3$ (590 mg, 7 mmol) at room temperature for 5 days. The solution was concentrated and chromatographed (SiO_2) to give a small amount of oligomeric product. However 50 % of the starting material (25 mg, 0.35 mmol) was recovered.

Isolation of Dimer 23 and Trimer of 2 :

A solution of **2** (50 mg, 0.7 mg) in chloroform (15 ml) was stirred at room temperature for 1 h. The solution was concentrated and chromatographed (SiO_2) to isolate the dimer (10 mg, 0.11 mmol), trimer (7 mg, 0.07 mmol), and tetramer (1 mg,

0.01 mg) in 15 %, 10 %, and 2 % yields, respectively and 70 % of monomer (35 mg, 0.49 mmol) was recovered.

The Dimer of 2 (23) : Brownish yellow plates; eluted with hexane/AcOEt = 90/10; mp 41-44 °C; IR (neat/cm^{-1}) 1740; The dimer was found to be a mixture of the isomers (73/27) by ^{1}H-NMR. ^{1}H-NMR for the major isomer (270 MHz, C_6D_6) δ 2.97 (s, 3H), 3.05 (s, 3H), 3.11 (s, 3H), 5.10 (s, 1H), 6.0-6.4 (m, 5H), 6.33 (s, 1H), 6.60 (s, 1H), 7.0-7.5 (m, 9H), 7.74 (dd, J = 7.3, 1.6 Hz, 2H), 8.24 (dd, J = 6.2, 1.1 Hz, 1H), 8.72 (dd, J = 5.9, 1.1 Hz, 1H); ^{1}H-NMR for the minor isomer (270 MHz, C_6D_6) δ 2.877 (s, 3H), 2.884 (s, 3H), 3.11 (s, 3H), 5.21 (s, 1H), 6.0-6.4 (m, 5H), 6.37 (s, 1H), 6.68 (s, 1H), 7.0-7.5 (m, 9H), 7.82 (dd, J = 7.3, 1.6 Hz, 2H), 8.35 (dd, J = 6.2, 1.1 Hz, 1H), 8.84 (dd, J = 5.9, 1.1 Hz, 1H); MS (EI) m/z 558 (11), 499 (100); HRMS Calcd. for $C_{35}H_{30}N_2O_5$ (M^+): 558.2156, Found: 558.2158.

The Trimer of 2 : Yellowish brown plates; eluted with hexane/AcOEt = 80/20; mp 111-113 °C; IR (neat/cm^{-1}) 1740; ^{1}H-NMR (90 MHz, C_6D_6) δ 2.8-3.2 (m, 12H), 5.13 (s, 1H), 5.8-6.6 (m, 10H), 6.68 (s, 1H), 6.8-7.2 (m, 14H), 7.7-7.9 (m, 2H), 8.10 (dm, J = 6.1 Hz, 1H), 8.38 (dm, J = 6.1 Hz, 1H), 8.76 (dm, J = 6.1 Hz, 1H); MS (EI) m/z 821 (71), 762 (100).

Basic Treatment of Oligomer 22

To a solution of **22** (20 mg) in THF (20 ml), ammonia gas was bubbled for 5 min. The solution was then bubbled with nitrogen gas for 30 min to purge excess ammonia and concentrated to give the hygroscopic yellowish brown solid.; IR (KBr/cm^{-1}) 1730.

Observation of pH Sensitive Behavior on UV-Vis. Spectra

A dioxane solution of **22** (1.33 g/l) and 0.5 M buffer solution (H_3BO_3-NaOH) which has prescribed pH value were mixed (1/10) and subjected to measurement on UV-Vis. spectrometer.

3-4. References

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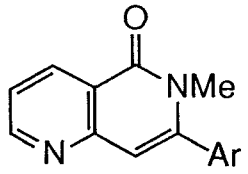
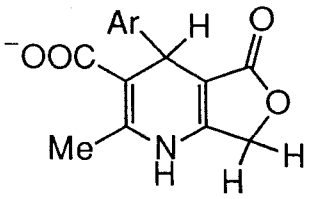
CHAPTER 4. SYNTHESIS OF [*b*]-FUSED PYRIDINES

4-1. Introduction

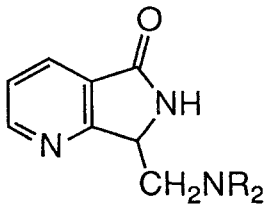
[*b*]-Fused pyridines are of great importance since these skeletons are often found in biologically active materials such as medicines and agrochemicals as shown below. However, there are few convenient preparative methods of these compounds because of restrictions in substituents or reaction conditions. Thus it is desired to develope new methods of functionalized pyrido compounds.



antiinflammatories[1)]

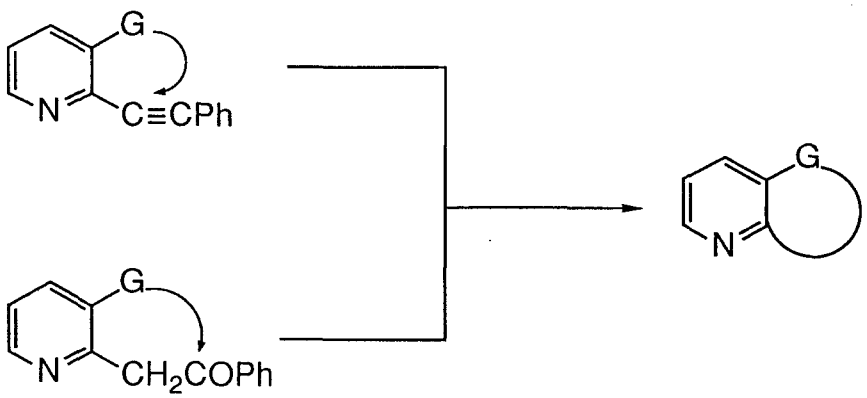


vasodilators[2)]



tranquilizers[3)]

The present ethynylation reaction, as mentioned in Chapter 1, is applicable to pyridines bearing reactive functional groups. Especially, vicinally functionalized pyridines are thought to form condensed heterocycles by intramolecular cyclization.[4)]

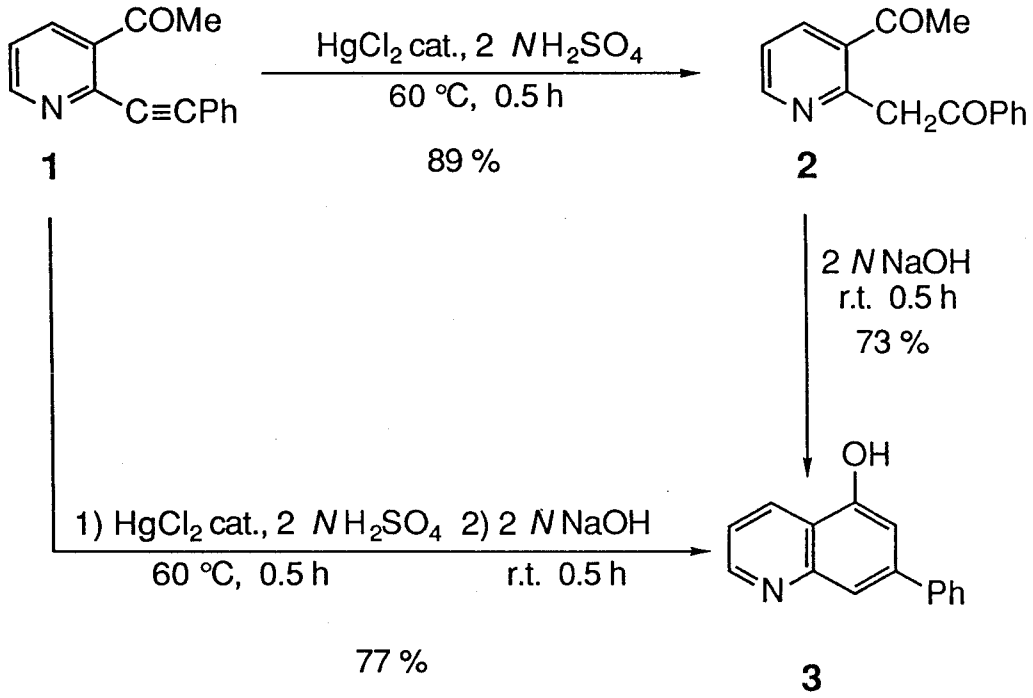


In this Chapter, various kinds of [*b*]-fused pyridines are synthesized from 2-phenylethynylpyridines which possess a functional group such as acetyl, cyano, and methoxycarbonyl group at 3-position. Since there are two ring closure manners to form five membered ring and six membered ring, some attempts to obtain one of these two ring systems selectively were also carried out.

4-2. Results and Discussion

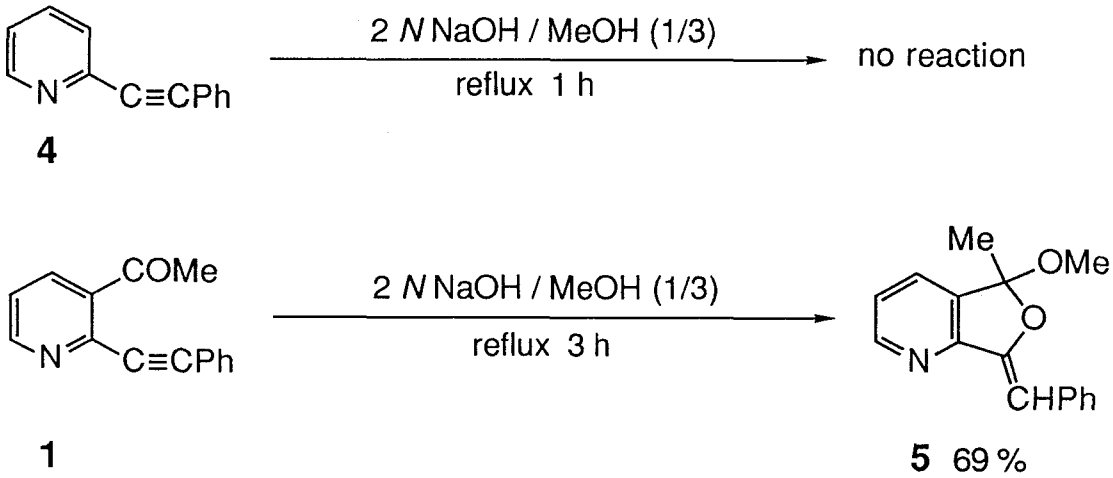
4-2-1. Cyclization of 3-Acetyl-2-phenylethynylpyridine

2-Phenylethynyl-3-acetylpyridine (**1**) was hydrated in 2*N* sulfuric acid in the presence of mercuric chloride to give 2-phenacyl-3-acetylpyridine (**2**) as mentioned in Chapter 2. The phenacylpyridine **2** readily underwent aldol condensation intramolecularly to give 7-phenyl-5-quinolinol (**3**) under basic conditions at room temperature.

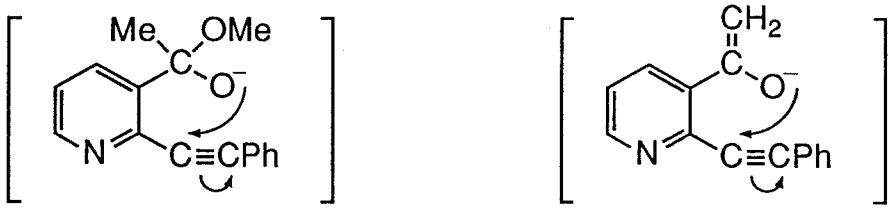


5-Quinolinol derivatives are used for additives of flotation of pyrochlore, mineral source of niobium and tantalum,[5] and their carbanilates are used for antilipolytic agents.[6] It was possible to obtain the quinolinol **3** directly from ethynylpyridine **1** by the same treatments in one pot.

In contrast, heating of 2-phenylethynylpyridine **4** under basic conditions caused no change in ethynyl group. Therefore cyclization of 3-substituted ethynylpyridines by intramolecular nucleophilic attack to the ethynyl function was studied under basic conditions. The acetyl derivative **1** afforded furo[3,4-*b*]pyridine **5** in a good yield under reflux in 2*N* sodium hydroxide / methanol (1/3).



Although furo[3,4-*b*]pyridine skeleton is often found in biologically active compounds, facile preparative methods for furopyridine are less known.[7),8] Among them, there are few reports[9] about synthesis of furopyridines bearing benzylidene group at 7-position. The configuration of the product was not determined but only one isomer was produced.



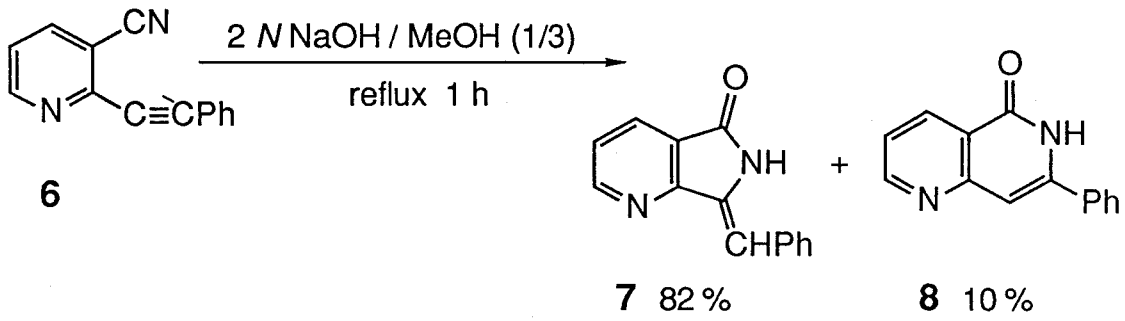
In this reaction, it is considered that the ring closure occurred after addition of methoxide anion to acetyl group and gave furopyridine **5**. However, possibility of the ring closure by attack of the enolate of acetyl group cannot be completely denied.

On the other hand, when tetrahydrofuran was used instead of methanol, no reaction occurred and ethynylpyridine **1** was recovered.

4-2-2. Cyclization of 3-Cyano-2-phenylethynylpyridine

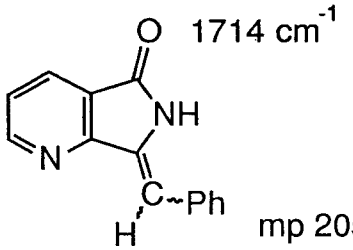
a) Synthesis of Pyrrolo[3,4-*b*]pyridine

The cyano derivative **6** afforded different products according to the reaction conditions. Thermal treatment of **6** in 2*N* sodium hydroxide / methanol (1/3) gave pyrrolo[3,4-*b*]pyridine **7**[10] in 82 % yield and 1,6-naphthyridin-5(6*H*)-one **8** in 10 % yield.



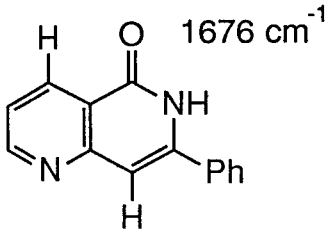
The structures of these pyrido compounds were determined by spectral and analytical data. In the IR spectra, the absorption of carbonyl group was observed at 1714 cm^{-1} for the pyrrolopyridine **7** and at 1676 cm^{-1} for the naphthyridinone **8**. In the case of naphthyridinone **8**, a long range coupling (i.e. cross ring coupling : J =

0.7 Hz) was observed between the protons at 4- and 8-positions in the ^{1}H-NMR spectrum.



mp 205 °C

δ 7.07

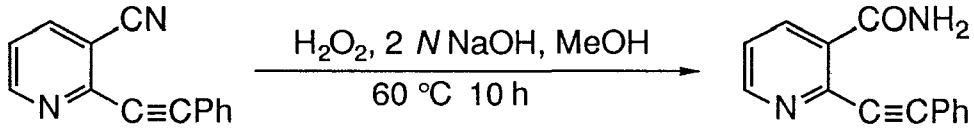


δ 7.06

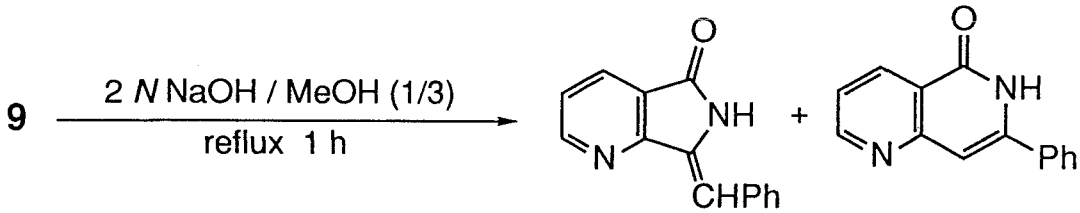
J = 0.7 Hz

mp 239 °C

The 3-carbamoyl pyridine **9** prepared by hydration of the 3-cyano pyridine **6** could be similarly converted to pyrrolopyridine **7** accompanied by naphthyridinone **8**. Hence, the carbamoyl pyridine **9** is assumed to be the precursor of the bicyclic pyridines **7** and **8** in the above mentioned reaction.

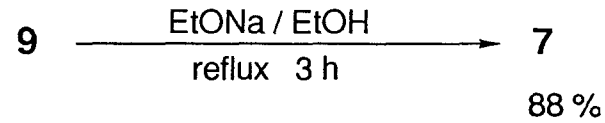


6 **9** 94 %



7 73 % **8** 18 %

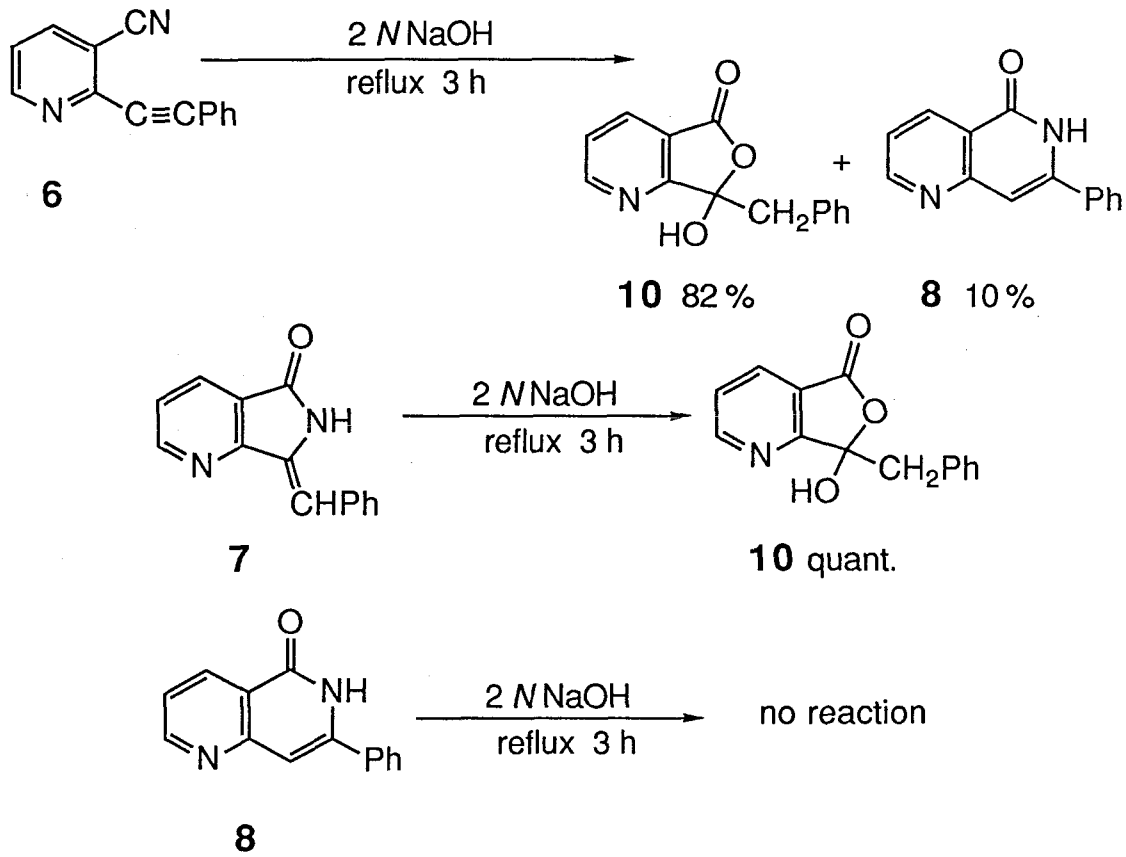
While it is reported that 2-phenylethynyl-3-carbamoyl-4,6-dimethylpyridine cyclizes to give a naphthyridinone derivative in a high yield when treated with sodium ethoxide in refluxing ethanol.[11] However, only pyrrolopyridine **7** and no naphthyridinone **8** was obtained from the 3-carbamoyl derivative **9** under the same conditions.



Furthermore, the structure of the pyrrolopyridine **7** was confirmed by the ozonolysis of **7** in chloroform giving pyrrolo[3,4-*b*]pyridine-5,7-dione[12] and benzoic acid.

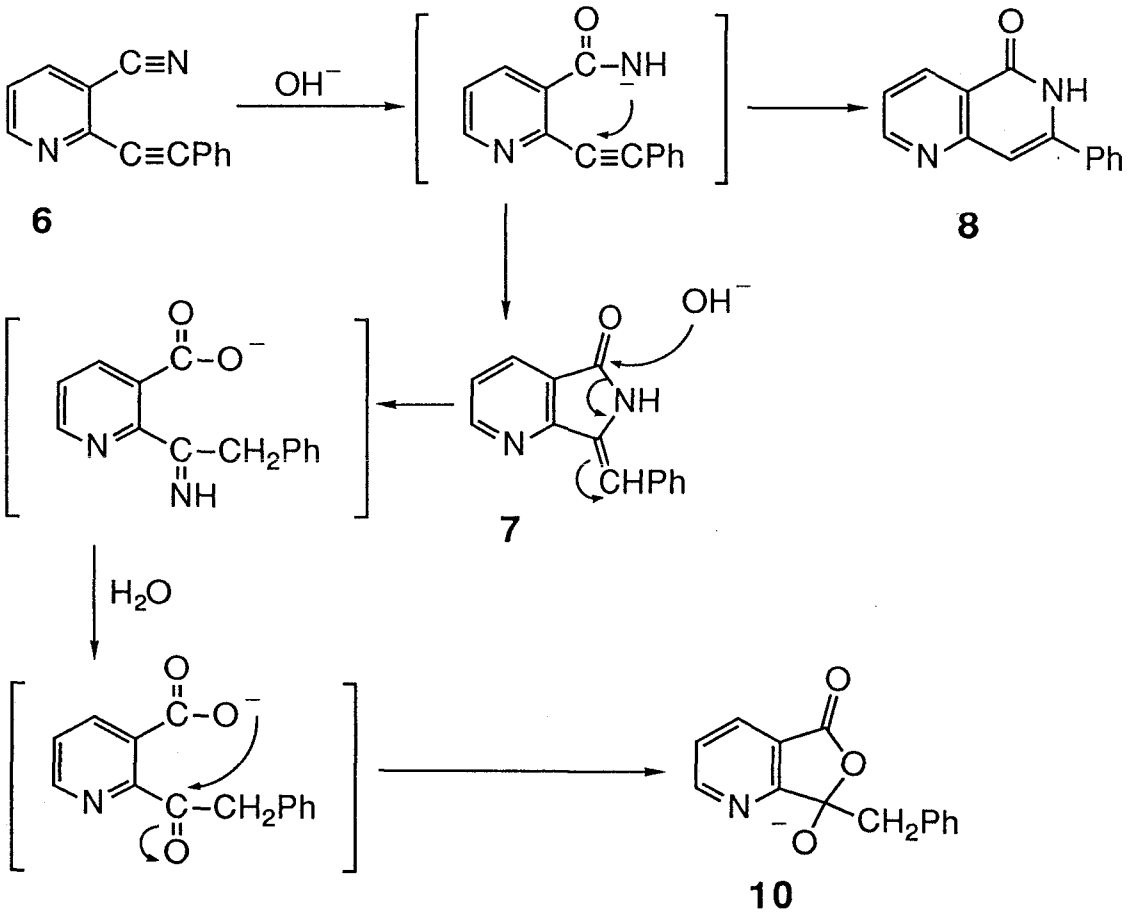
b) Synthesis of Furo[3,4-*b*]pyridine

On the other hand, the treatment of the pyridine **6** in 2*N* sodium hydroxide gave three products, pyrrolopyridine **7**, furo[3,4-*b*]pyridine **10**[10] and naphthyridinone **8**, in earlier stage of this reaction. After reflux for three hours, furopyridine **10** was mainly obtained together with a minor amount of the naphthyridinone **8**.



The furopyridine **10** is considered to be formed via pyrrolopyridine **7** which was quantitatively transformed to **10** in refluxing 2*N* sodium hydroxide, but naphthyridinone **8** caused no change under the same conditions.

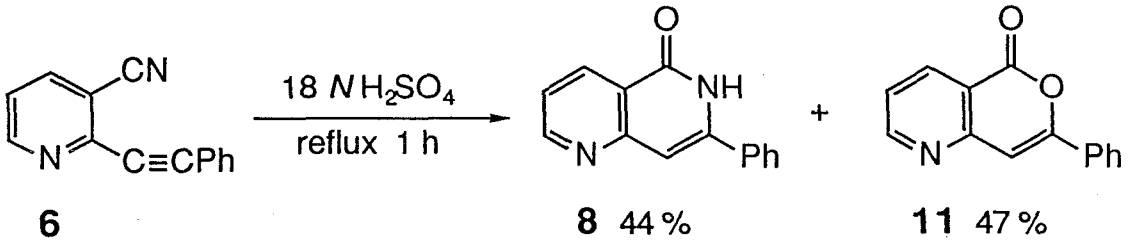
Hence, from the above results, the present reaction is thought to proceed as follows. The amide anion produced by the attack of hydroxide ion to cyano group intramolecularly cyclizes to give the pyrrolopyridine **7** and the naphthyridinone **8**. To the carbonyl group of the pyrrolopyridine, hydroxide ion attacks and recyclizes to afford the furopyridine **10**, but further transformation of the naphthyridinone **8** does not occur because of its stability.



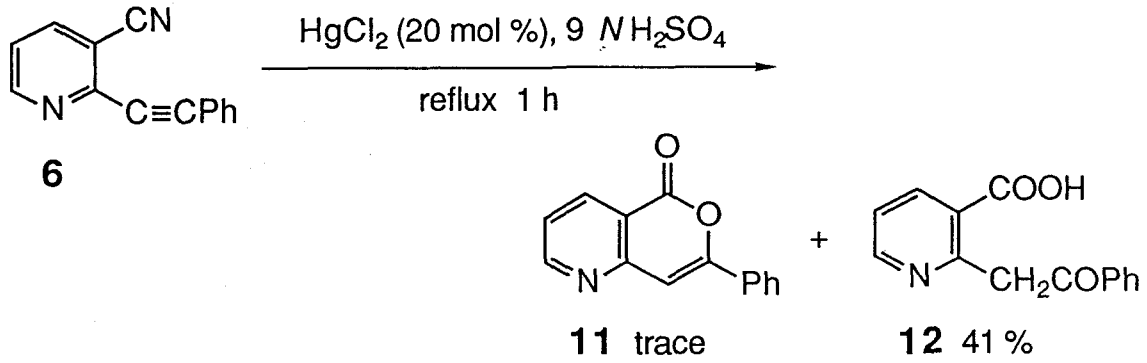
c) Synthesis of 1,6-Naphthyridin-5(6*H*)-ones

1,6-Naphthyridin-5(6*H*)-ones are important compounds because of their biological activities such as muscle relaxing,[1] antiinflammatory,[1] antibacterial,[13] and antimalarial activities,[14] etc. However, the known synthetic methods[15),16] for them suffer from some restrictions. As mentioned in Section **a**, the cyclization of 2-phenylethynyl-3-cyanopyridine **6** gave only a small amount of naphthyridinone **8**. Hence, the cyclization of cyano derivative **6** under acidic conditions was investigated.

Ethynylpyridine **6** was heated in 18 *N* sulfuric acid under reflux to afford 1,6-naphthyridin-5(6*H*)-one **8** and pyrano[4,3-*b*]pyridin-5-one **11**[17),18] in 44 % and 47 % yields, respectively. In the case of the reaction in 2 *N* or 9 *N* sulfuric acid, the starting compound **6** was almost recovered.

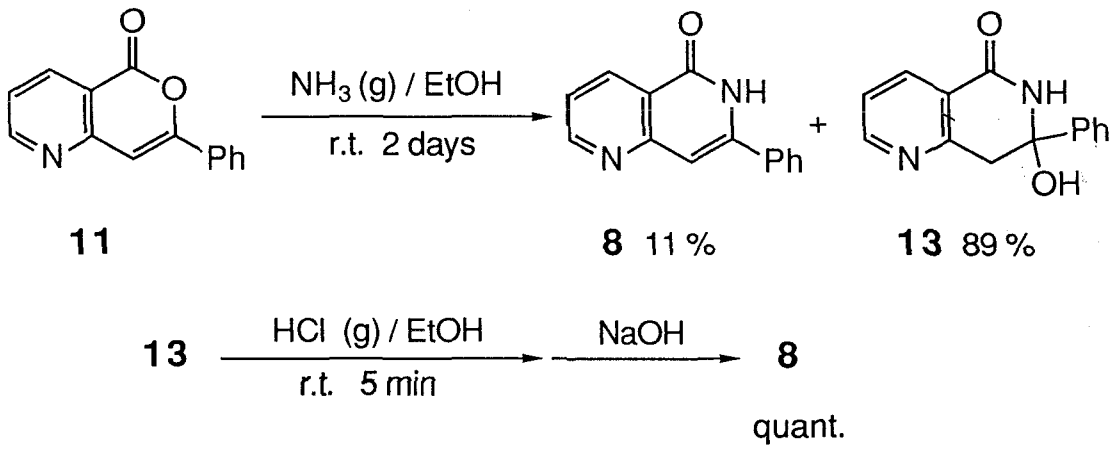


On the other hand, both hydration of the triple bond and hydrolysis of cyano group underwent in the presence of mercuric chloride as a catalyst in 9 *N* sulfuric acid,[17] and 2-phenacylpyridine-3-carboxylic acid **12** was obtained along with a trace amount of pyranopyridine **11**.



d) Transformation of Pyrano[4,3-*b*]pyridine to 1,6-Napthyridin-5(6*H*)-ones

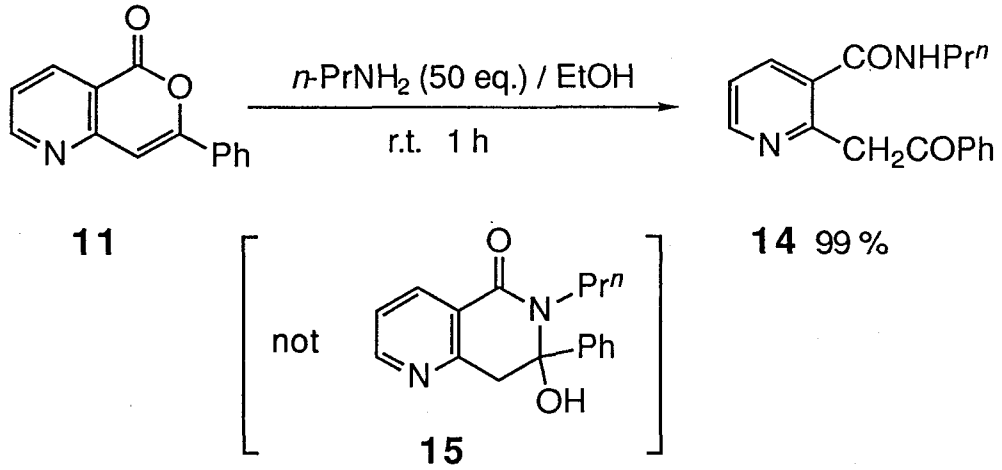
Wibberley reported a conversion method of pyranopyridine **11** *into* naphthyridinone **8**,[19] similar treatment of **11** with ammonia gas in ethanol mainly produced dihydronaphthyridinone **13**[20] and the expected naphthyridinone **8** was obtained only in a very low yield. Being bubbled hydrogen chloride gas into an ethanol solution of the dihydro derivative **13**,[1] dehydration proceeded to give naphthyridinone **8** quantitatively.



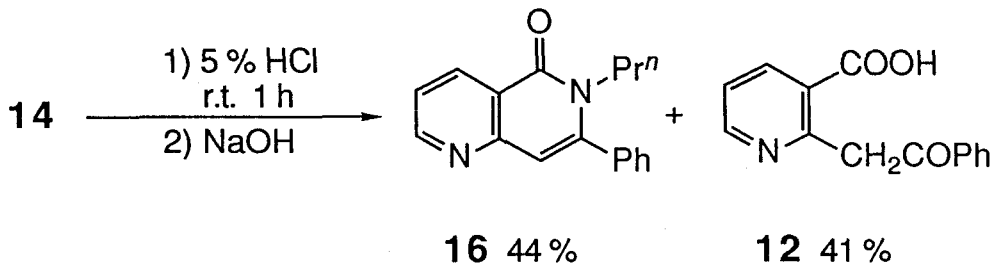
It was found that this reaction does not need such a long reaction time as that by Wibberley nor bubbling of ammonia and hydrogen chloride gases. Thus the reaction of **11** with 50 eq. of aqueous ammonia in ethanol readily underwent even in one hour to form **13** which was successively converted to naphthyridinone **8** in one pot.

These results show that pyrano[4,3-*b*]pyridine **11** is equivalent to 1,6-naphthyridin-5(6*H*)-one **8**.

Furthermore, synthesis of naphthyridinone bearing an alkyl substituent at 6-position from pyranopyridine **11** was examined by treatment with propylamine instead of ammonia. Contrary to the expectation, the product was phenacylpyridine **14** without formation of the anticipated dihydronaphthyridinone **15**.



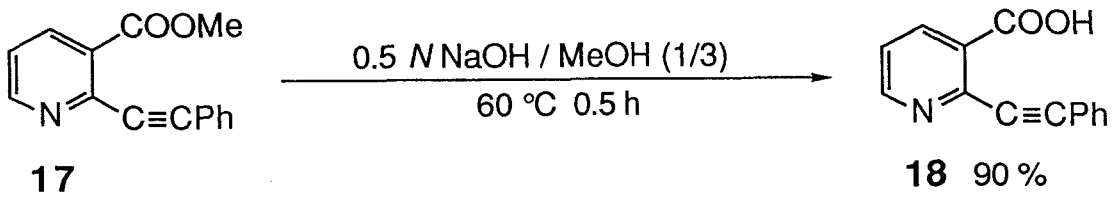
Successive treatment of **14** with hydrochloric acid caused ready cyclization to form 6-propyl-7-phenyl-1,6-naphthyridin-5(6*H*)-one (**16**). In this reaction, no change was observed when sodium hydroxide was used as a cyclizing reagent.[1)]



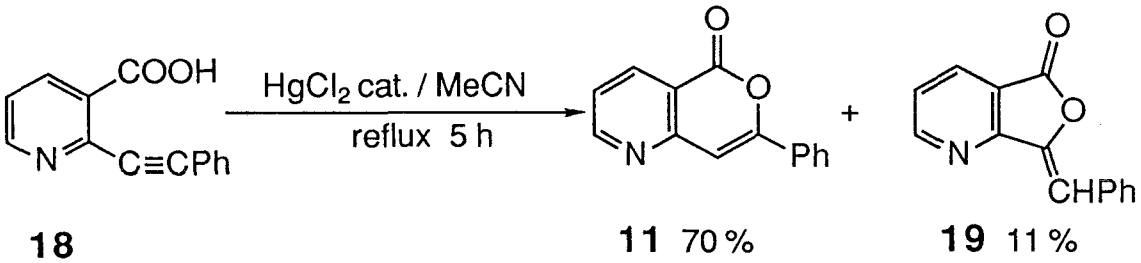
Since it is also possible to convert nicotinic acid **12** into the 1,6-naphthyridin-5(6*H*)-ones,[21)] ethynylpyridine **6** would be the useful synthetic intermediate of naphthyridinones. Furthermore, the reaction leading to 6-alkylated naphthyridinone[21),22)] is expected to be applicable to syntheses of a variety of 6-substituted derivatives.

4-2-3. Cylization of Ethynylnicotinic Acid

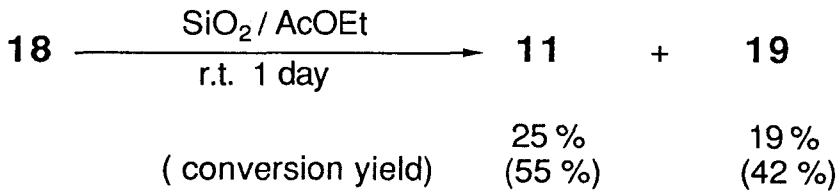
Alkaline hydrolysis of the 3-methoxycarbonyl-2-phenylethynylpyridine (**17**) gave 2-phenylethynylnicotinic acid (**18**) in a good yield.



The obtained nicotinic acid **18** was readily transformed to pyrano[4,3-*b*]pyridine **11**[17),18)] along with a small amount of furo[3,4-*b*]pyridine **19**[9)] by heating in the presence of a catalytic amount of mercuric chloride. Pyrano[4,3-*b*]pyridine is a pharmacologically important skeleton as an aza homolog of isocoumarin and as a synthetic intermediate of 1,6-naphthyridin-5-one as mentioned in Section **4-2-2**.

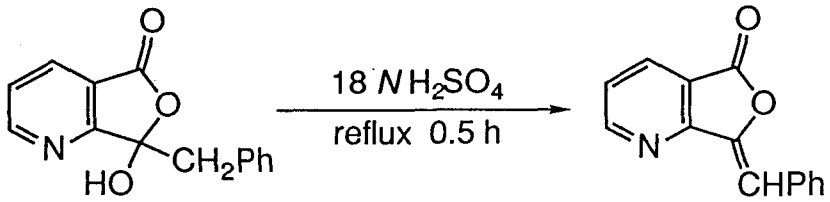


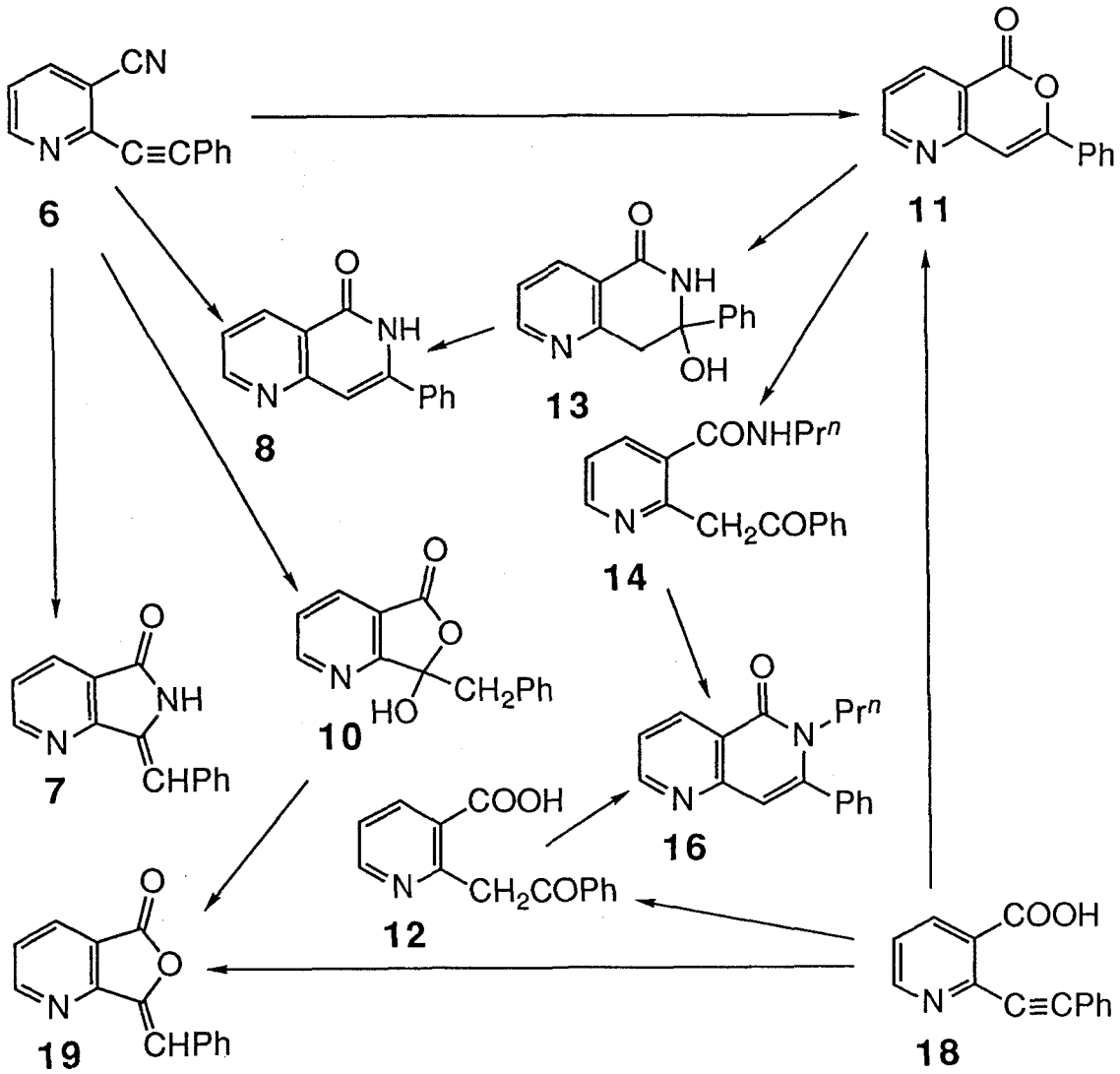
The ratio of the furopyridine **19**, which was minor product in the above reaction, could be slightly raised by stirring with silica gel at in ethyl acetate room temperature. However, a large amount of starting material was recovered after the reaction, since this reaction was too slow.



Thus development of the other synthetic routes to furopyridine **19** was investigated. As the furopyridine **10** obtained from 2-phenylethynyl-3-cyanopyridine **6** was the hydrated form of the furopyridine **19**, dehydration reaction of **10** was

examined. Dehydration readily underwent in refluxing 18 *N* sulfuric acid to afford the furopyridine **19** in a good yield.



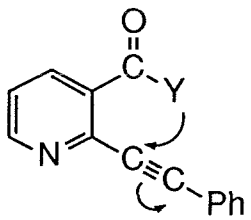


From the results mentioned in Sections **4-2-2** and **4-2-3**, it was clarified that 2-phenylethynyl-3-cyanopyridine **6** and 2-phenylethynylpyridine-3-carboxylic acid **18** are the valuable synthetic intermediates for various [*b*]-fused bicyclic pyridines. It was noteworthy that the some pyrido compounds such as naphthyridinone **8**, pyranopyridine **11** and furopyridine **19** were synthesized from both of ethynylpyridines **6** and **18**. The whole correlations of them are summarized in above scheme. Thus it would be expected to obtain the further functionalized polycyclic pyridines.

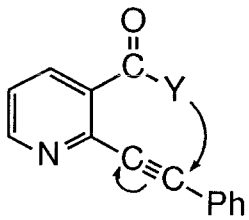
4-2-4. Orientation of the Intramolecular Cyclization

In the present cyclizations, five membered bicyclic pyridines were obtained as main products under basic conditions and six membered ones were obtained as main products under acidic conditions or in the presence of mercuric chloride. These orientation of cyclization are explained as follows.

Under basic conditions, endo type cyclization is considered to be difficult because of the outer carbon of the ethynyl group is situated far from the substituent at 3-position because of its linear structure.



major



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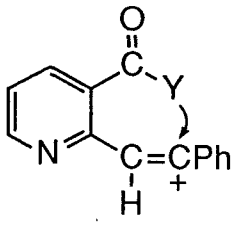
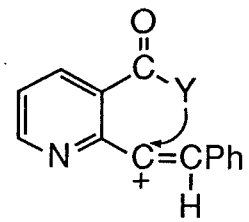


major



minor

While under acidic conditions, ethynyl group has a cationic and sp^2 characters, while make it possible for the ethynylgroup to bent considerably. Hence the intramolecular attack to the more stable carbon predominantly proceeded to form six menbered ring.

4-3. Experimental

General

Melting points are uncorrected. Mass spectra were obtained using a HITACHI RMU-6E (70 eV), a JEOL JMS-DX 303, and a Shimadzu GCMS-QP2000 mass spectrometer. High resolution mass spectrum (HRMS) was recorded with a JEOL JMS-DX303 mass spectrometer. IR spectra were recorded on a Hitachi 270-30 infrared spectrometer and NMR spectra were measured on a JEOL FT-NMR JMN FX90Q at 90 MHz and a JEOL FT-NMR GSX at 270 MHz with TMS as an internal standard. Elemental analyses were performed on Yanagimoto CHN-Corder Mt-2.

Intramolecular Aldol Condensation of 2-Phenacyl-3-acetylpyridine 2

A solution of 2-phenacyl-3-acetylpyridine **2** (50 mg, 0.21 mmol) in 2 *N* NaOH (5 ml) was stirred at room temperature for 0.5 h and neutralized with hydrochloric acid to afford white precipitates. The reaction mixture was extracted with CH_2Cl_2 (4 x 10 ml). The extract was dried ($MgSO_4$) and concentrated to give 5-quinolinol **3** (34 mg, 0.15 mmol).

7-Phenyl-5-quinolinol (3) : milky white solid; mp 229-235 °C; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 7.1-7.9 (m, 8H), 8.50 (md, J = 8.6 Hz, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 153.8, 151.0, 149.2, 141.7, 140.0, 130.4, 130.4, 129.1, 128.0, 127.0, 120.0, 119.0, 117.0, 107.6; MS (EI) m/z 221 (100), 220 (13).

A Typical Procedure for Cyclization under Basic Conditions

A solution of cyano substituted ethynylpyridine **6** (100 mg, 0.5 mmol) in 2*N* NaOH (10 ml) was refluxed for 3 h and the reaction mixture was extracted with CH_2Cl_2 (4 x 15 ml). The extract was dried over $MgSO_4$ and concentrated to give naphthyridinone **8** (11 mg, 0.05 mmol). After acidified with dil. HCl, the aqueous layer was extracted with CH_2Cl_2 (4 x 15 ml) and the extract was dried ($MgSO_4$) and concentrated to give only furopyridine **10** (99 mg, 0.41 mmol).

The other bicyclic pyridines were synthesized with similar treatment. When methanol was used for the solvent, methanol was evaporated before the extraction.

6,7-Dihydro-5-methoxy-5-methyl-7-benzylidene-5*H*-furo[3,4-*b*]pyridine (5) : pale yellow oil; IR (neat/ cm^{-1}) 1668, 1026; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.86 (s, 3 H), 3.03 (s, 3H), 6.48 (s, 1H), 7.1-7.5 (m, 4H), 7.74 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.8-8.0 (m, 2 H), 8.67 (dd, *J* = 4.8, 1.7 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 154.1, 151.9, 150.6, 135.3, 132.5, 130.5, 129.0, 128.4, 126.5, 123.1, 110.8, 99.4, 50.3, 26.0; MS (EI) *m/z* 253 (19), 238 (100), 222 (15), 220 (27).

6,7-Dihydro-7-benzylidene-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (7) : colorless needles; mp 205-206 °C; IR (KBr/cm^{-1}) 3232, 1714; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.07 (s, 1H), 7.3-7.6 (m, 6H) 8.18 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.5 (br, 1H), 8.84 (dd, *J* = 5.0, 1.4 Hz, 1H); ^{13}C-NMR (90 MHz, CDCl3) δ 167.0, 156.8, 153.6, 134.5, 132.0, 131.6, 129.1, 129.0, 128.2, 123.5, 122.5, 108.4; MS (EI) *m/z* 222 (43), 221 (100); Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; O, 7.20. Found: C, 75.50; H, 4.48; N, 12.50.

7-Phenyl-1,6-naphthyridin-5(6*H*)-one (8) : colorless needles; mp 239-240 °C (lit.[21] 229-230 °C); IR (KBr/ cm^{-1}) 3060, 1676; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.06 (d, *J* = 0.7 Hz, 1H), 7.40 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.5-7.9 (m, 5H), 8.66 (ddd, *J* = 8.1, 1.9, 0.7 Hz, 1H), 8.94 (dd, *J* = 4.8, 1.9 Hz, 1H), 9.9-10.2 (br, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 163.9, 155.2, 154.9, 143.4, 135.7, 133.8, 130.2, 129.3, 126.4, 121.4, 120.9, 106.1; MS (EI) *m/z* 222 (100); Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; O, 7.20. Found: C, 75.69; H, 4.41; N, 12.50.

6,7-Dihydro-7-benzyl-7-hydroxy-5*H*-furo[3,4-*b*]pyridin-5-one (10) : pale yellow plates; mp 115-117 °C; IR (KBr/cm^{-1}) 3128, 1770; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.6-3.9 (bs, 2H), 4.5-5.5 (br, 1H), 7.1 (s, 5H), 7.46 (dd, J = 7.6, 5.2 Hz, 1H), 8.03 (dd, J = 7.6, 1.7 Hz, 1H), 8.83 (dd, J = 5.2, 1.7 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 166.7, 163.0 (br), 153.6, 135.3, 132.9, 130.4, 130.1, 128.3, 127.2, 125.2, 122.8, 44.5; MS (EI) m/z 241 (35), 223 (28), 222 (38), 150 (100), 122 (37), 106 (42), 92 (72), 91 (47); Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81; O, 19.90. Found: C, 69.70; H, 4.48; N, 5.81.

Cyclization of Ethynylpyridine 6 under Acidic Conditions

Ethynylpyridine **6** (102 mg, 0.5 mmol) was heated in 18 *N* H_2SO_4 (10 ml) under reflux for 1 h. NaOHaq. was added to the reaction mixture and extracted with CH_2Cl_2 (30 ml x 4) under the weakly acidic or neutral conditions. If the reaction mixture was basified, pyranopyridine **11** would be decomposed.[19] The organic layer was dried ($MgSO_4$) and concentrated. The crude product was separated by column chromatography (SiO_2) eluted with hexane/AcOEt (3:1) to give **11** as colorless plates; yield: 52 mg (47 %); mp 135-136°C and hexane/AcOEt (1:3) to give **8** as colorless needles; yield : 49 mg (44 %); mp 239-240 °C.

7-Phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one : colorless plates; mp 135-136 °C (lit.[17] 134-135 °C); IR (KBr/cm^{-1}) 1738; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.22 (d, J = 0.7 Hz, 1H), 7.3-7.6 (m, 4H), 7.7-8.0 (m, 2H), 8.54 (ddd, J = 8.1, 2.0, 0.7 Hz, 1H), 8.93 (dd, J = 4.9, 2.0 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 161.8, 157.3, 156.3, 155.0, 137.5, 131.4, 130.7, 129.0, 125.6, 122.8, 116.9, 103.6; MS (EI) m/z 223 (100), 195 (51), 105 (38), 77 (38); Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27; O, 14.33. Found: C, 75.36; H, 3.99; N, 6.25.

2-Phenacylpyridine-3-carboxylic acid (12) : Ethynylpyridine **6** (102 mg, 0.5 mmol) was heated in 9 *N* H_2SO_4 (10 ml) under reflux for 1 h in the presence of $HgCl_2$ (27 mg, 0.1 mmol). The reaction mixture was extracted with CH_2Cl_2 (30 ml x 4). The extract was dried ($MgSO_4$) and concentrated. The crude product was chromatographed on a silica gel column using $CHCl_3$/AcOEt (1:1) as an eluent to

give **5**. The product was recrystalized from $CHCl_3$/MeOH to give colorless needles; yield: 77 mg (64 %); mp 180°C (dec.) (lit.[21] 175-177°C).

Reaction of Pyranopyridine 11 and Ammonia (or Propylamine)

A solution of 25 % NH_3aq. (1.7 g, 25 mmol) in EtOH (5 ml) was added to a solution of pyranopyridine **11** (112 mg, 0.5 mmol) in EtOH (6 ml) and stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was recrystalized from CH_2Cl_2 to give **13** (102 mg, 0.43 mmol).

7-Hydroxy-7-phenyl-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one (13) : colorless plates; mp 181-184°C (dec.); IR (KBr/cm^{-1}) 3416, 1688; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.35 (brs, 1H), 3.50 (s, 2H), 6.57 (brs, 1H), 7.2-7.8 (m, 6H), 8.36 (dd, J = 7.6, 1.4 Hz, 1H), 8.63 (dd, J = 5.2, 1.4 Hz, 1H); MS (EI) m/z 222 (100), 77 (20); The compound was too susceptible to dehydration to obtain satisfactory microanalysis.

***N*-Propyl-2-phenacylpyridine-3-carboxamide (14)** : yellow plates; mp 94-95 °C; IR (neat/cm^{-1}) 3292, 1692, 1640; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.77 (t, J = 7.3 Hz, $3H^e$), 0.93 (t, J = 7.3 Hz, $3H^k$), 1.4-1.8 (m, $2H^e$ + $2H^k$), 3.33 (dt, J = 7.0, 6.2 Hz, $2H^k$), 3.46 (dt, J = 7.0, 6.2 Hz, $2H^e$), 4.77 (s, $2H^k$), 6.3-6.5 (br, $1H^e$), 6.51 (s, $1H^e$), 7.0-7.2 (br, $1H^k$), 7.2-7.9 (m, $6H^e$ + $4H^k$), 7.85 (dd, J = 7.8, 1.6 Hz, $1H^k$), 8.11 (dd, J = 8.6, 1.4 Hz, $2H^k$), 8.32 (dd, J = 7.8, 1.6 Hz, $1H^e$), 8.43 (dd, J = 4.9, 1.6 Hz, $1H^e$), 8.55 (dd, J = 4.9, 1.6 Hz, $1H^k$), 15.5-15.8 (br, $1H^e$) (H^e: enol form, H^k: keto form); ^{13}C-NMR (270 MHz, $CDCl_3$) δ 198.8, 168.2, 164.3, 154.6, 152.9, 152.0, 150.2, 145.4, 142.2, 136.5, 135.7, 135.7, 133.7, 129.6, 128.7, 128.4, 125.9, 125.7, 124.3, 122.6, 121.0, 117.8, 88.8, 46.0, 45.5, 41.8, 22.8, 22.6, 11.5, 11.3; MS (EI) m/z 282 (2), 196 (17), 105 (100), 77 (64); Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; O, 11.33. Found: C, 71.96; H, 6.53; N, 9.86.

Cyclization of Pyridine-3-carboxamide 14

Phenacylpyridinecarboxamide **14** (140 mg, 0.5 mmol) was dissolved in 5 % HCl (25 ml) and stirred for 1 h at room temperature. The reaction mixture was basified with NaOH and extracted with CH_2Cl_2 (30 ml x 4). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified with column

chromatography (SiO_2) using hexane/AcOEt (95:5) as an eluent to give naphthyridinone **16** (58 mg, 0.22 mmol). The aqueous layer was acidified with 2 *N*HCl and extracted with CH_2Cl_2 (30 ml x 4). The extract was dried ($MgSO_4$) and concentrated to give 2-phenacylpyridine-3-carboxylic acid (**22**) (50 mg, 0.19 mmol).

6-Propyl-7-phenyl-1,6-naphthyridin-5(6*H*)-one (14) : pale yellow oil; IR (neat/cm^{-1}) 1654, 1622; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.74 (t, J = 7.4 Hz, 3H), 1.4-1.8 (m, 2H), 3.8-4.0 (m, 2H), 6.68 (d, J = 0.6 Hz, 1H), 7.38 (dd, J = 8.1, 4.6 Hz, 1H), 7.3-7.6 (m, 5H), 8.71 (ddd, J = 8.1, 1.9, 0.6 Hz, 1H), 8.90 (dd, J = 4.6, 1.9 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 162.9, 154.5, 152.8, 147.6, 136.2, 135.7, 129.1, 128.7, 128.5, 121.4, 117.3, 109.4, 47.2, 22.0, 11.0; MS (EI) m/z 264 (11), 263 (18), 222 (100); HRMS Calcd. for $C_{17}H_{16}N_2O$: 264.1263, Found: 264.1289.

Cyclization of Ethynylpyridine-3-carboxylic Acid 18

A solution of ethynylpyridine-3-carboxylic acid (110 mg, 0.5 mmol) and $HgCl_2$ (3 mg, 0.01 mmol) in acetonitrile (12 ml) was refluxed for 5 h and concentrated. The reaction mixture was chromatographed to afford pyranopyridine **11** (78 mg, 0.35 mmol) and furopyridine **19** (11 mg, 0.05 mmol).

Dehydration of Furopyridine 10

A solution of furopyridine **10** (120 mg, 0.5 mmol) in 18 *N* H_2SO_4 (12 ml) was heated under reflux for 0.5 h. NaOHaq. was added to the reaction mixture and extracted with CH_2Cl_2 (30 ml x 4) to give furopyridine **19** (89 mg, 0.4 mmol).

6,7-Dihydro-7-benzylidene-5*H*-furo[3,4-*b*]pyridin-5-one (19) : colorless needles; mp 127-128 °C; IR (KBr/cm^{-1}) 1780; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.96 (s, 1H), 7.3-7.6 (m, 4H), 7.8-8.0 (m, 2H), 8.23 (dd, J = 7.8, 1.7 Hz, 1H), 8.91 (dd, J = 4.8, 1.7 Hz, 1H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 164.7, 158.6, 156.2, 143.8, 133.7, 132.6, 130.8, 129.1, 128.8, 124.1, 117.4, 108.8; MS (EI) m/z 223 (65), 222 (100); Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27; O, 14.33. Found: C, 75.44; H, 4.11; N, 6.30.

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CONCLUSION

In this thesis, it was investigated to synthesize polyfunctionalized pyridine derivatives which were important key compounds for the development of functional heterocyclic systems containing nitrogen atoms.

In Chapter 1, the ethynylation of pyridine ring utilizing Reissert-Henze salt was studied. It was found that the direct ethynylation proceeded regioselectively. Although the reaction conditions should be optimized to get better yields, one of the most important natures of this reaction is applicability to various acetylenes and wide range of pyridines including those having reactive substituents such as acetyl, cyano and methoxycarbonyl groups. Hence, the present reaction is useful method for polyfunctionalization of pyridine derivatives.

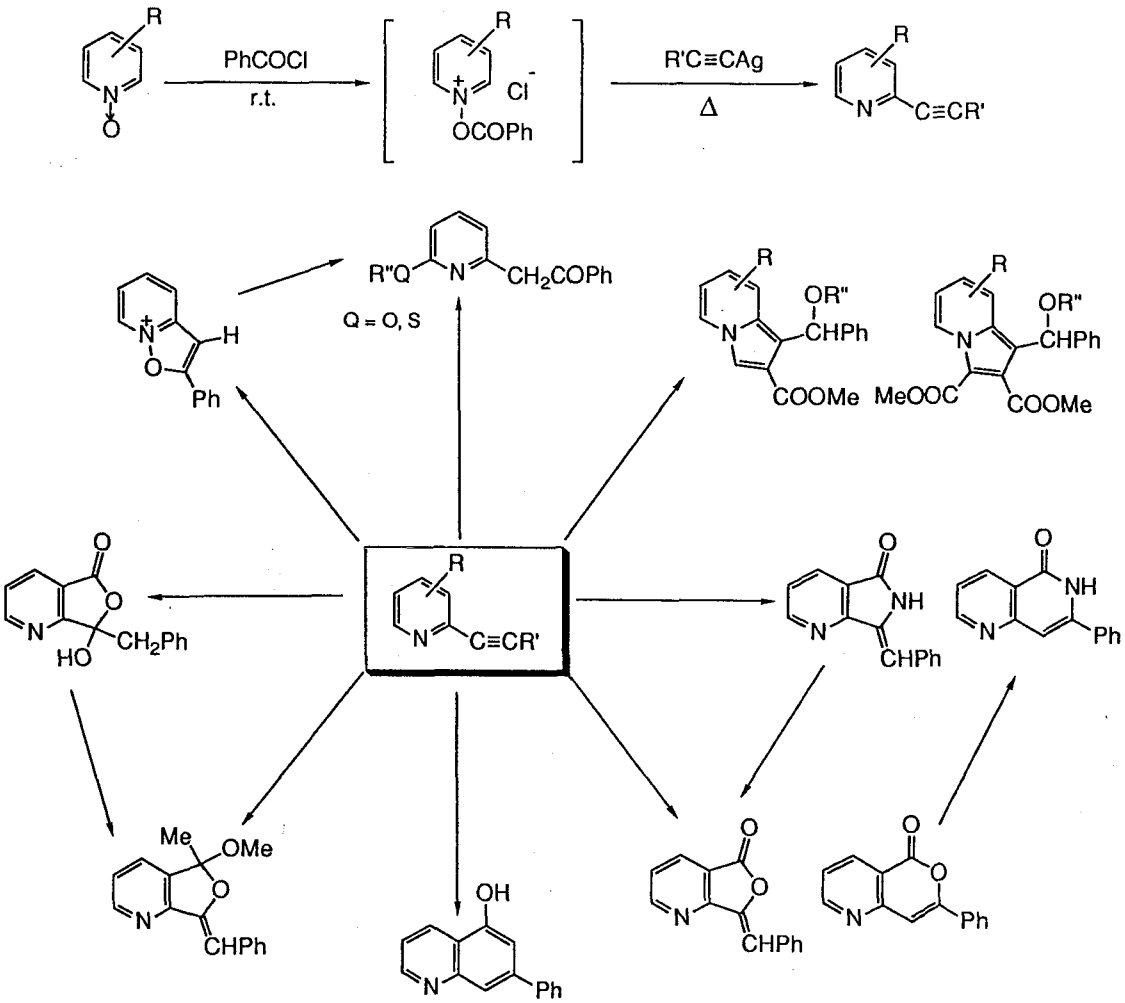
In Chapter 2, the synthesis of functionalized phenacylpyridines were examined. It was clarified the hydration was applicable to phenylethynylpyridines possesing acetyl group and functionalized phenacylpyridines were produced. Meanwhile, the oxidation of ethynylpyridine was investigated to get a precursor for polyethynylation. Although the desired *N*-oxide was not obtained, it was found that the functionalization at 6-position of 2-phenacylpyridines was possible via oxidation and that isoxazolo[2,3-*a*]pyridinium salt was formed as an intermediate of this reaction.

In Chapter 3, indolizine derivatives were synthesized, which constitute a representative ring system of [*a*]-fused bicyclic pyridines. It was found that ethynylpyridines gave indolizine derivatives bearing functional group by cycloaddition with dimethyl acetylenedicarboxylate. Furthermore, the oligomerization of indolizine derivative was found and it was clarified that the color of the oligomer was changed depending on pH.

In Chapter 4, various [*b*]-fused bicyclic pyridines were synthesized by intramolecular cyclization of vicinally difunctionalized pyridines. From these results, it was clarified that vicinally functionalized ethynylpyridines or

phenacylpyridines are the useful synthetic intermediates of bicyclic pyridines. The orientation of cyclization to form five membered ring or six membered one was also studied and it was succesful to obtain the minor product on a cyclizing reaction as a major product in other reaction procedure.

Most of polyfunctionalized pyridines which were obtained in these studies are hitherto unknown compounds or are synthesized with difficulties. The pyridine derivatives, ethynylpyridines, phenacylpyridines and [*a*] or [*b*] fused bicyclic pyridines, are expected to be applied to functional materials such as medicines, agricultural chemicals, dyes, ligands and so on. Hence, the each reaction founds in these studies would be one of useful synthetic methods of polyfunctionalized pyridines.



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