Functionalization of Pyridines via Reissert-Henze Reaction

Yoshiki Ohshiro* and Hiroshige Kikuta**
Kinki University, Kowakae, Higashi-Osaka 577, Japan
**Research Institute for Science and Technology*
***Faculty of Science and Technology*

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Abstract

Reaction of Reissert-Henze salt with silver acetylide gave the pyridine ethynylated selectively at 2-position. 2-(Phenylethynyl)pyridines substituted 3-position with a carbonyl or masked carbonyl group were converted to various bicyclic pyridine derivatives by intramolecular cyclization. 3-Cyano-2-(phenylethynyl)pyridine was cyclized intramolecularly under acidic conditions to give the naphthyridine and pyranopyridine derivatives. 2-(Phenylethynyl)pyridine reacted with dimethyl acetylenedicarboxylate in the presence of a proton source to give indolizines having methoxycarbonyl groups at the 2- or 2,3-positions.

Key words: Heterocycle, Pyridine, Fused Pyridine, Reissert-Henze Salt

1 Introduction

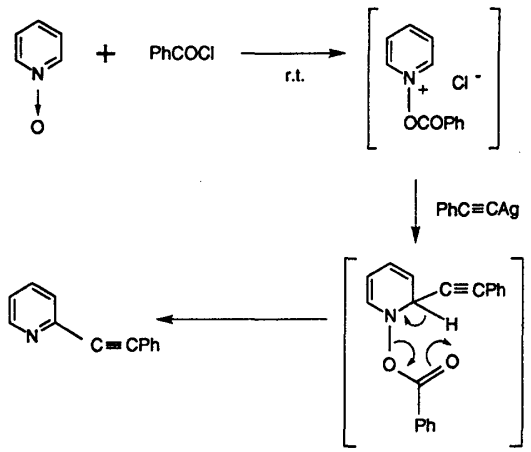
It is of great importance to develop facile methods for introducing functional groups to a pyridine ring in terms of synthesis of polyfunctionalized pyridines. Introduction of an ethynyl group possessing versatile reactivity is highly valuable, but the known direct ethynylation methods [1-7] suffer from some restrictions. As Reissert-Henze salt, N-acyloxypyridinium salt, has a good leaving group, nucleophilic attack of an acetylide to the salt is expected to give ethynylated pyridine derivatives. One of the advantages of this method is its applicability to pyridines having reactive substituents such as acetyl, cyano, and methoxycarbonyl groups. The functionalized ethynylpyridines are known to be useful as synthetic intermediates. Especially, vicinally functionalized pyridines such as 3-substituted 2-ethynyl derivatives are thought to form condensed heterocycles by intramolecular cyclization.

2 Ethynylation of pyridines [8]

A typical procedure is as follows. Benzoyl chloride (1.5 equivalent) was added to a solution of pyridine N-oxide (1.5 equivalent) at room temperature to generate N-benzoyloxypyridinium salt. It is so difficult to isolate the salt because of its hygroscopic character[9] that the reaction was carried out without isolation of the salt. After stirring for 0.5 h, silver phenylacetylide (1.0 equivalent) was added and the reaction mixture was heated for 1 h. 2-(Phenylethynyl)pyridine was isolated from the reaction mixture.

Only 2-ethynylation was observed without any formation of 4-(phenylethynyl)pyridine. Nonpolar solvents were more suitable than polar solvents to avoid side reactions. The reaction was performed at 60 through 80° for 1 h.

It is supposed that the reaction proceeds with attack of the pyridine ring to form 1,2-dihydropyridine intermediate followed by elimination of benzoic acid intramolecularly.

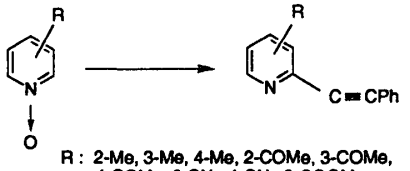


(Scheme 1)

This reaction could be applied to other type of acetylenes. Silver acetylides having functional groups such as ether and ester groups reacted under similar conditions, and the corresponding ethynylpyridines were produced in rather low yields.

Application of this method to N-oxides of other pyridine homologs, such as quinoline, isoquinoline, and pyrimidine, was also possible. In each case, ethynylation occurred only at alpha-position of the nitrogen atoms, and 3-ethynylated isoquinoline and 6-ethynylated pyrimidine were not detected.

In order to synthesize polyfunctionalized pyridines, substituted pyridine N-oxides were adapted in this ethynylation. In all cases, the substitution occurred at 2- or 6-position and not at 4-position. Electron-withdrawing substituents raised the yields of ethynylpyridines.



R : 2-Me, 3-Me, 4-Me, 2-COMe, 3-COMe, 4-COMe, 3-CN, 4-CN, 3-COOMe

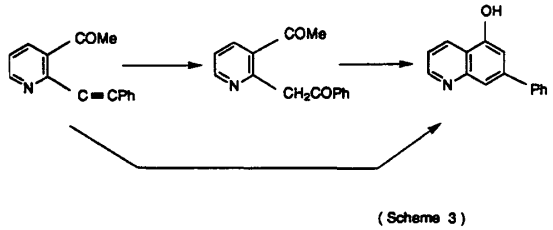
(Scheme 2)

When the 3-substituted pyridine N-oxides were used as substrates, ethynylation occurred at 2- and 6-positions, but 2-ethynylation was predominant in all cases. The higher reaction temperature and polarity of solvents gave rise to higher regioselectivity of the 2-substituted pyridines.

3 Syntheses of [b]-Fused Bicyclic pyridines [10,11]

3-Substituted 2-ethynylpyridines are thought to form condensed heterocycles by intramolecular cyclization [12].

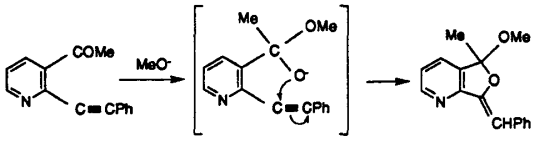
2-Phenacyl-3-acetylpyridine, which was obtained from 2-(phenylethynyl)-3-acetylpyridine by hydration in 2N sulfuric acid in the presence of mercury(II) chloride, readily underwent aldol condensation to give 7-phenyl-5-quinolinol under basic conditions at room temperature. It was possible to obtain the quinolinol directly from ethynylpyridine by the same treatment in one pot.



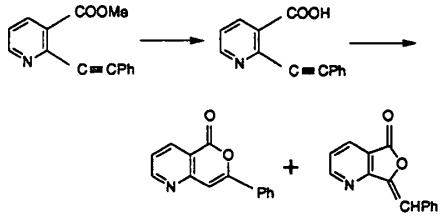
(Scheme 3)

2-(Phenylethynyl)-3-acetylpyridine afforded furo[3,4-b]pyridine via 2-phenacyl-3-acetylpyridine under reflux in methanolic sodium hydroxide solution.

Alkaline hydrolysis of 3-methoxycarbonyl-2-(phenylethynyl)pyridine gave 2-(phenylethynyl)-nicotinic acid, which was transformed to pyrano[4,3-b]pyridine along with a small amount of the furo[3,4-b]pyridine derivative by heating in acetonitrile in the presence of a catalytic amount of mercury(II) chloride.

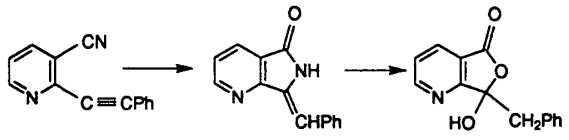


(Scheme 4)



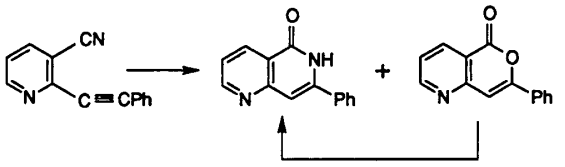
(Scheme 5)

3-Cyano-2-(phenylethynyl)pyridine afforded different products according to reaction conditions. Thermal treatment of the cyano derivative in methanolic sodium hydroxide solution gave the pyrrolo[3,4-b]pyridine derivative, and this compound transformed to the furo[3,4-b]pyridine derivative.



(Scheme 6)

On the contrary, 3-cyano-2-(phenylethynyl)-pyridine gave 7-phenyl-1,6-naphthyridin-5(6H)-one and 7-phenyl-5H-pyrano[4,3-b]pyridin-5-one by refluxing in 18N sulfuric acid. The latter compound could be transformed to the former compound by treatment with ammonia followed by acidification with hydrochloric acid.

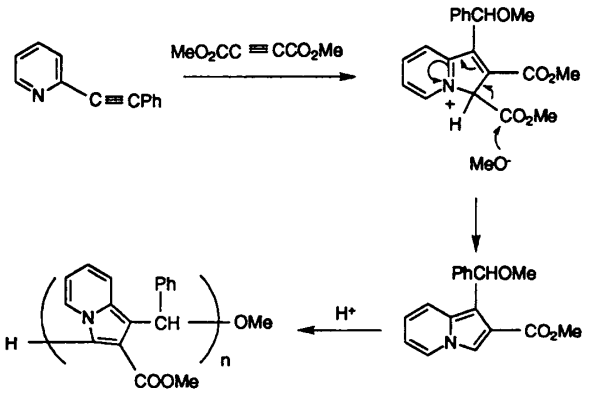


(Scheme 7)

In the cyclization reactions, bicyclic pyridines fused five membered ring were obtained as major products under basic conditions, and pyridines fused six membered ring were obtained as major products under acidic conditions.

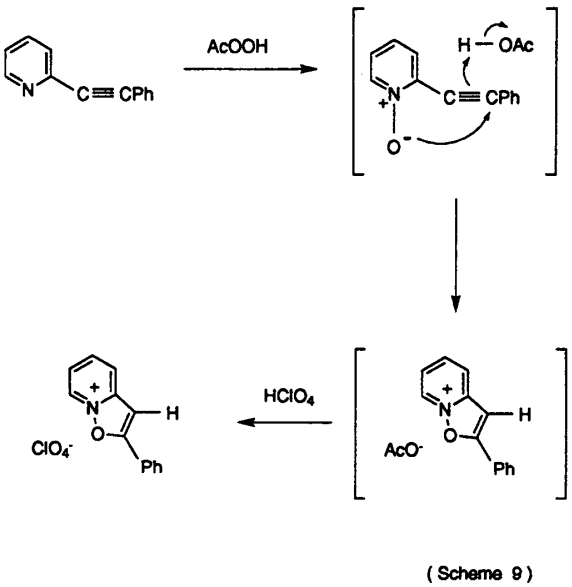
4 Syntheses of [a]-Fused Bicyclic pyridines [13,14]

A benzene solution of 2-(phenylethynyl)-pyridine, methanol, and dimethyl acetylenedicarboxylate was stirred at room temperature for one day. 1-(Metoxybenzyl)-2-methoxycarbonylindolizine was isolated from the reaction mixture. This indolizine derivative was readily oligomerized at room temperature in chloroform containing trace amount of acid. The oligomer was evaluated as a pH sensitive dye.



(Scheme 8)

In the reaction of 2-(phenylethynyl)pyridine with peracetic acid, the formation of 2-phenylisooxazolo[2,3-a]pyridinium acetate was observed. Although this compound was unstable, it was able to isolate as a perchlorate salt.



(Scheme 9)

5 Conclusion

Chemical transformations of ethynylpyridines were developed 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 and indolizine derivatives are applied to various functional materials such as biologically active compounds, dyes, and synthetic intermediates of polycyclic systems.

Especially, [b]-fused pyridines are pharmacologically interesting compounds and most of them are synthesized from vicinally bifunctional pyridines.

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