CHEMISTRY LETTERS, pp. 773-776, 1989.

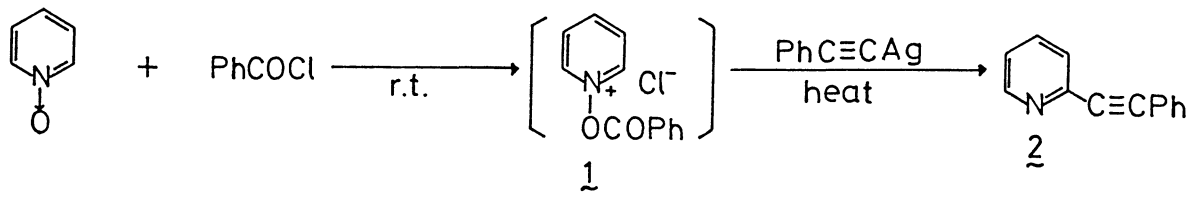
A Novel Ethynylation of Pyridines by Reissert-Henze Type Reaction

Nagatoshi NISHIWAKI, Satoshi MINAKATA, Mitsuo KOMATSU, and Yoshiki OHSHIRO*
Department of Applied Chemistry, Faculty of Engineering,
Osaka University, Suita, Osaka 565

Reaction of N-benzoyloxypyridinium chloride, Reissert-Henze salt, with silver acetylide gave the pyridine ethynylated selectively at 2-position. The reaction is applicable to various substituted pyridines and pyridine homologs.

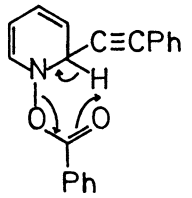
It is of great importance to develop facile methods for introducing functional groups to a pyridine ring in terms of synthesis of polyfunctionalized pyridines. Especially introduction of an ethynyl group possessing versatile reactivity is highly valuable, but the known direct ethynylation methods[1] 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. It was found that silver acetylide was most successful for the present purpose. We wish to report here the novel ethynylation reaction utilizing the Reissert-Henze salt.

A typical procedure is as follows. Benzoyl chloride (1.5 equiv.) was added dropwise to a solution of pyridine N-oxide (1.5 equiv.) in a solvent at room temperature to generate N-benzoyloxypyridinium salt 1 as white precipitates. It is so difficult to isolate the salt because of its hygroscopic character[2] that the reaction was carried out without isolation of the salt. After stirring for 0.5 h, silver phenylacetylide (1.0 equiv.) was added and the reaction mixture was heated for 1 h. Insoluble material was filtered off and the filtrate was washed (2 mol dm^{-3} NaOHaq), dried ($MgSO_4$) and concentrated in vacuo to give 2-phenylethynylpyridine 2, which was isolated by column chromatograpy (Al_2O_3, hexane/benzene = 1/1).



1 2

Only α-ethynylation was observed without any formation of 4-phenylethynylpyridine, the γ-ethynylated product, and the results are shown in Table 1. Nonpolar solvents were more suitable than polar solvents to avoid side reactions. The reaction was performed at 60 through 80 °C for 1 h, and



3

higher temperature or prolonged reaction time caused no positive effect.

Table 1. Ethynylation of pyridine N-oxide

RC≡CAg	Solv.	Temp/°C	Time/h	Yield/%[a]
R = Ph	c-Hex	80	1	40
"	"	60	"	42
"	"	"	5	43
"	"	40	1	22
"	n-Hex	70	"	44
"	PhH	80	"	35
"	"	"	"	35[b]
"	"	"	"	trace[c]
"	THF	67	"	18
"	DMF	60	"	5
"	DMSO	"	"	0
R = CH_2OTHP	PhH	80	"	22
R = COOMe	"	"	"	20

a)Determined by ^{1}H-NMR. b)NEt_3(1.5 equiv.) was added. c)DBU(1.5 equiv.) was added and many products were obtained.

It is supposed that the reaction proceeds with attack of the acetylide to the pyridine ring to form 1,2-dihydropyridine intermediate 3 followed by elimination of benzoic acid. Bases were added in order to accelerate the elimination of proton at 2-position from the adduct 3 and to trap benzoic acid, but no effect appeared. Thus the elimination of benzoic acid from 3 is considered to proceed intramolecularly.

This reaction could be applied to other types 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 (Table 1). From these results, the present method is applicable to other acetylides and the introduction of various substituted ethynyl groups is expected.

Table 2. Ethynylation with metal acetylides

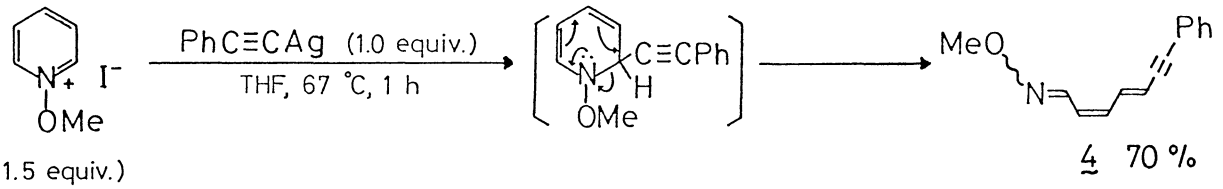
PhC≡CM	Yield/%[a]
M = Ag	42
Cu	11
Na	0[b]
MgBr	22
$SiMe_3$	0[c]
$SnMe_3$	0[c]

a)Reactions were carried out in c-hexane at 60 °C for 1 h. b)PhCOC≡CPh was obtained. c)PhC≡CH was recovered.

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 silver acetylide. In the case of a sodium acetylide, a more ionic acetylide, benzoyl(phenyl)acetylene arising from attack to the benzoyloxy moiety of 3 was obtained. Trimethylsilyl or trimethyltin phenylacetylide did not give the ethynylpyridine 2 but phenylacetylene was recovered.

As salt forming reagents, benzoyl bromide, p-toluoyl chloride, benzene sulfonyl chloride, and pivaloyl chloride showed similar reactivity as that of benzoyl chloride. Acetyl chloride showed lower reactivity and acetic anhydride gave no ethynylpyridine 2. Methyl iodide did not form the corresponding quaternary salt under the conditions used for the acyl halides, but the salt was formed by the known method.[3] Reaction of the isolated N-methoxypyridinium iodide with silver phenylacetylide gave the acyclic product 4, and no ethynylated pyridine.[4] 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 is exclusive. Though ring closure of the azatriene 4 by heating in the presence of p-toluenesulfonic acid was examined, only isomerization of 4 occurred.



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

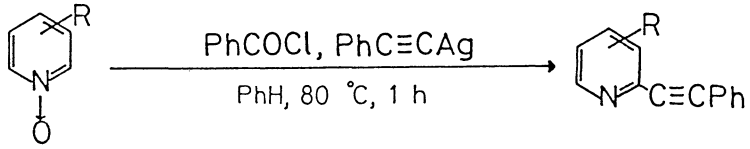
Table 3. Ethynylation of N-oxides of pyridine homologs[a)]

Substrate	Product	Yield/%
Quinoline 1-oxide	2-phenylethynylquinoline	21
Isoquinoline 2-oxide	1-phenylethynylisoquinoline	30[b)]
Pyrimidine 1-oxide	2-phenylethynylpyrimidine	10

a)Reactions were carried out in a similar manner to that of pyridine N-oxide. (PhH, 80 °C, 1 h) b)c-Hex, 60 °C, 1 h

In order to synthesize polyfunctionalized pyridines, substituted pyridine N-oxides were employed in this ethynylation and results are listed in Table 4.

Table 4. Ethynylation of substituted pyridine N-oxides



Substrate(R)	Product(R)	[Ratio][a)]	Total yield/%[a)]
2-Me	6-Me	———	30[b)]
3-Me	3-Me/5-Me	[83/17]	39
4-Me	4-Me	———	25
3-Et	3-Et/5-Et	[70/30]	36
2-COMe	2-COMe	———	50
3-COMe	3-COMe/5-COMe	[67/33]	47
4-COMe	4-COMe	———	51
3-CN	3-CN/5-CN	[56/44]	60
4-CN	4-CN	———	50
3-COOMe	3-COOMe/5-COOMe	[52/48]	47

a)Determined by ^{1}H-NMR.

b)2-Pyridylmethyl benzoate was obtained in 40% yield.

In all cases, the substitution occurred at 2- or 6-position and not at 4-position. Electron-withdrawing substituents raised the yields of ethynylpyridines. It was found that hitherto unknown polyfunctionalized ethynylpyridines can be easily prepared by this method.[5)]

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. Detailed study on this selectivity is in progress.

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. This method is useful for polyfunctionalization of pyridines and polyfunctionalized ethynylpyridines thus obtained are expected as synthetic intermediates for condensed heterocycles and so on.[6)]

References

1) T. Agawa and S. I. Miller, J. Am. Chem. Soc., 83, 449 (1961); R. Yamaguchi, Y. Nakazono, T. Matsuki, and M. Kawanisi, Bull. Chem. Soc. Jpn., 60, 215 (1987); R. Yamaguchi, E. Hata, and K. Utimoto, Tetrahedron Lett., 29, 1785 (1988); K. Sonogashira, Y. Tohda, and N. Hagihara, ibid., 1975, 4467; S. Takahashi, Y. Kuroyama, K. Sonogashira, and N. Hagihara, Synthesis, 1980, 627; H. Yamanaka, M. Shiraiwa, K. Edo, and T. Sakamoto, Chem. Pharm. Bull., 27, 270 (1979); T. Sakamoto, M. Shiraiwa, Y. Kondo, and H. Yamanaka, Synthesis, 1983, 312.

2) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York (1971), p.159.

3) E. Ochiai, M. Katada, and T. Naito, Yakugaku Zasshi, 64, 210 (1944).

4) Similar ring opening reaction using ArMgBr was reported; T. J. van Bergen and R. M. Kellog, J. Org. Chem., 36, 1705 (1971); U. Fitzsche and S. Hünig, Justus Liebigs Ann. Chem., 1974, 1407

5) All the products were isolated and gave satisfactory spectral data. The spectral data for acetyl derivatives, for example, are as follows. 2-phenylethynyl-3-acetylpyridine: 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), and 8.74 (dd, J=4.8, 2.1 Hz, 1H); MS (m/z) 221 (M^+, 100%), 206 (M^+-Me, 39%), 178 (M^+-COMe, 39%). 2-phenylethynyl-5-acetylpyridine: 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), and 9.0-9.2 (m, 1H); MS (m/z) 221 (M^+, 100%), 206 (M^+-Me, 89%), 178 (M^+-COMe, 27%).

6) Applications of the ethynylated pyridines to synthesis of condensed heterocycles are under investigation.

(Received February 15, 1989)