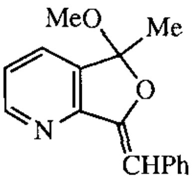
EFFECTIVE SYNTHESIS OF 7-BENZYLIDENEFURO[3,4-*b*]PYRIDIN-5-ONE

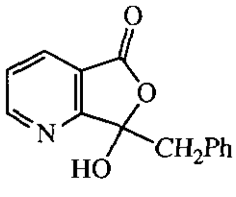
Nagatoshi Nishiwaki, Mitsuo Komatsu, and Yoshiki Ohshiro*
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565, Japan

Abstract - The title compound (**5**) was synthesized by silica gel assisted cyclization of 2-phenylethynylpyridine-3-carboxylic acid (**3**). It was also synthesized from 3-cyano-2-phenylethynylpyridine (**6**) in good yield by basic cyclization and dehydration processes.

Vicinally functionalized ethynylpyridines[1] are useful intermediates for bicyclic pyridine syntheses,[2,3] and we have clarified that various pyrido compounds such as 5-hydroxyquinoline, furo[3,4-*b*]pyridines, pyrano[4,3-*b*]pyridine, pyrrolo[3,4-*b*]pyridine and 1,6-naphthyridin-5(6*H*)-ones were easily synthesized from ethynylpyridines.[2] Among them, furo[3,4-*b*]pyridine skeleton is often found in the biologically active compounds[4] and pressure sensitive recording materials.[5] However, efficient preparative methods for the furopyridines are less known.[6]

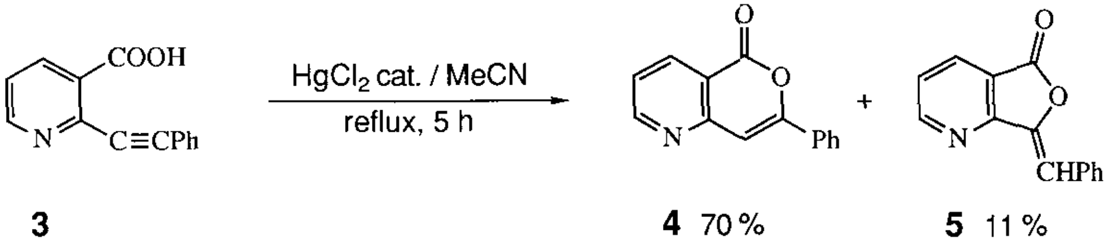


1



2

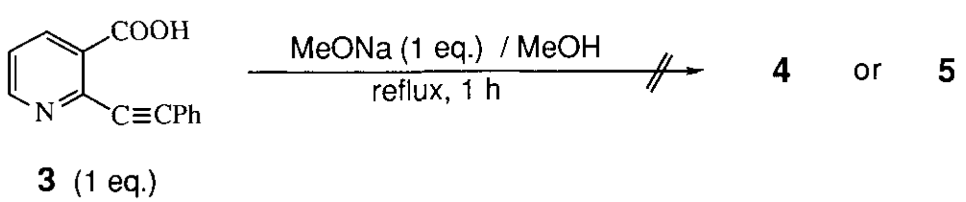
In a previous paper,[2] we reported that furopyridines (**1**) and (**2**) could be synthesized in good yields, and furopyridine (**5**)[7] having a benzylidene group was obtained only as a by-product in the cyclization of 2-phenylethynylpyridine-3-carboxylic acid (**3**) to pyranopyridne (**4**)[7] in the presence of mercuric chloride.



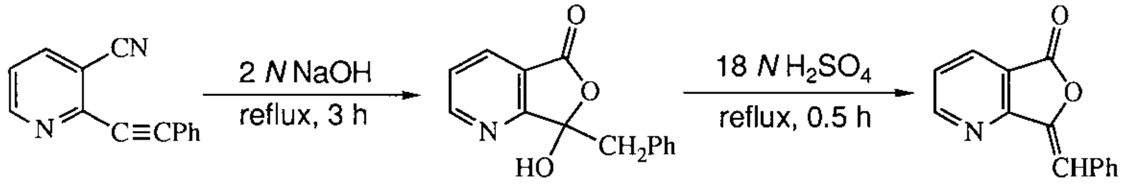
$$3 \xrightarrow[60\ °C,\ 1day]{SiO_2\ (pH\ 6.8)\ /\ AcOEt} \underset{52\ \%}{\mathbf{4}} + \underset{33\ \%}{\mathbf{5}}$$

In this paper, we wish to report that the silica gel assisted cyclization of the pyridinecarboxylic acid (**3**) is an effective synthetic method of the furopyridine (**5**). A solution of carboxylic acid (**3**) and silica gel in ethyl acetate was heated at 60 °C for 1 day to afford the pyranopyridine (**4**) and the furopyridine (**5**) in 52 and 33 % yields, respectively. The reaction was influenced by conditions such as the nature of solvent, reaction temperature, and acidity of silica gel.[8] No products other than **4** and **5** were formed and the furopyridine (**5**) was easily separated from the starting material (**3**) and the pyranopyridine (**4**) by means of extraction and column chromatography.

In the cyclization of 3-substituted ethynylpyridines, five membered ring formation was generally predominant over six membered ring formation under basic conditions,[2] but no cyclization of sodium salt of the acid (**3**) was observed.



As another synthetic path, the dehydration of the furopyridine (**2**) which was easily synthesized from 3-cyano-2-phenylethynylpyridine (**6**) was tried. Treatment of **2** with refluxing 18 *N* H_2SO_4 gave the furopyridine (**5**) in 80 % yield.



6 **2** **5** 80 %

Furo[3,4-*b*]pyridines bearing an alkylidene group at the 7-position are synthetically interesting compounds having several reactive sites and also biologically interesting ones. Though few facile preparative methods are known,[9] these two routes are effective synthetic methods of 7-benzylidenefuro[3,4-*b*]pyridin-5-one (**5**).

EXPERIMENTAL

Silica Gel Assisted Cyclization

A mixture of the carboxylic acid (**3**) (112 mg, 0.5 mmol) and silica gel (pH 6.8, 4.5 g) in AcOEt (11.2 ml) was heated at 60 °C for 1 day. Silica gel was filtered off and the filtrate was washed with saturated aq. $NaHCO_3$ (10 ml). The organic layer was dried ($MgSO_4$), concentrated and the residue was chromatographed to give 7-phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (**4**) (58 mg, 0.26 mmol) and 6,7-dihydro-7-benzylidene-5*H*-furo[3,4-*b*]pyridin-5-one (**5**) (37 mg, 0.17 mmol) respectively (eluted with hexane/AcOEt = 80/20). Unreacted carboxylic acid (**3**) was recovered (17 mg, 0.08 mmol) from aqueous layer by extraction with CH_2Cl_2 (10 ml x 4) upon acidification with hydrochloric acid.

Dehydration of Furopyridine (**2**)

A solution of 6,7-dihydro-7-benzyl-7-hydroxy-5*H*-furo[3,4-*b*]pyridin-5-one (**2**) (120 mg, 0.5 mmol) in 18 *N* H_2SO_4 (12 ml) was refluxed for 0.5 h. 2*N* aq. NaOH was added to the reaction mixture and extracted with CH_2Cl_2 (30 ml x 4). The organic layer was dried ($MgSO_4$), concentrated and the residue was chromatographed to give the furopyridine (**5**) (89 mg, 0.4 mmol, eluted with hexane/AcOEt = 70/30).

REFERENCES AND NOTES

1. N. Nishiwaki, S. Minakata, M. Komatsu, and Y. Ohshiro, *Chemistry Lett.*, **1989**, 773.
2. a) N. Nishiwaki, S. Minakata, M. Komatsu, and Y. Ohshiro, *Synlett*, **1990**, 273. b) N. Nishiwaki, M. Komatsu, and Y. Ohshiro, *Synthesis*, **1991**, 41.
3. T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1988, **27**, 2225.
4. a) S. Goldmann, R. Gross, M. Bechem, M. Kayser, M. Schramm, and S. Hebisch, *Ger. Offen.*, DE 3,706,204 (1988) (*Chem. Abstr.*, 1989, **110**, 173208). b) S. D. Young, *U. S. Pat.* 4,567,268 (1986) (*Chem. Abstr.*, 1986, **105**, 42769). c) Y. Sato, H. Fujita, S. Kumakura, and H. Takagi, *Japan. Kokai*, 77,153,994 (1977) (*Chem. Abstr.*, 1978, **88**, 152593).
5. a) D. Bedekovic and I. J. Fletcher, *Ger. Offen.*, DE 3,416,767 (1983) (*Chem. Abstr.*, 1985, **102**, 63602). b) Matsushita Electric Industrial Co., Ltd., *Jpn. Tokkyo Koho*, 80 12,593 (1980) (*Chem. Abstr.*, 1980, **93**, 195495). c) Hodogaya Chemical Co., Ltd. and Fuji Photo Film Co., Ltd., *Ger. Offen.*, 2,435,640 (1975) (*Chem. Abstr.*, 1975, **83**, 69144).
6. a) T, Goto, M. Saito, and R. Sato, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4178. b) H. Nagano, Y. Nawata, and M. Hamana, *Chem. Pharm. Bull.*, 1987, **35**, 4068. c) W. R. Ashcroft, M. G. Beal, and J. A. Joule, *J. Chem. Soc.,Perkin Trans. 1*, **1981**, 3012.
7. The obtained bicyclic pyridines gave satisfactory spectral and analytical data (See reference 2).
8. Fuji Davison M. B. Silica gels were used (100-200 mesh); MB-3A (pH 4.2), MB-4B (pH 6.8), MB-5D (pH 8.0).
9. a) L. E. Neiland and G. Ya. Vanag, *Chem. Heterocycl. Compounds*, 1967, **3**, 81 (Translated from *Khim. Geterotsikl. Soedin*). b) A. A. Artamonov, L. I. Timoshenko, G. M. Musienko, and L. P. Klimok, *Chem. Heterocycl. Compounds*, 1982, **18**, 843. c) A. S. Kende, J. E. Veits, D. P. Lorah, and F. H. Ebetino, *Tetrahedron Lett.*, 1984, **25**, 2423.

Received, 18th March, 1991