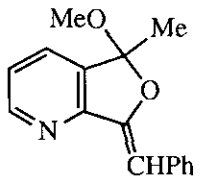
EFFECTIVE SYNTHESIS OF 7-BENZYLIDENEFURO[3,4-*b*]PYRIDIN-5-ONE

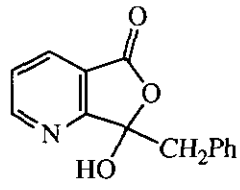
Nagatoshi Nishiwaki, Mitsuo Komatsu, and Yoshiki Ohshiro*
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565, Japan

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]

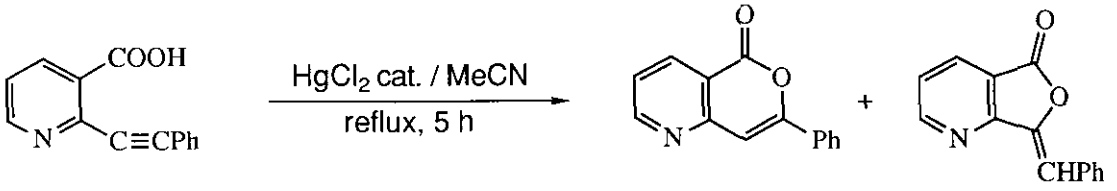


1

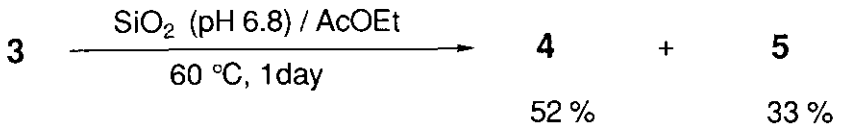


2

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.

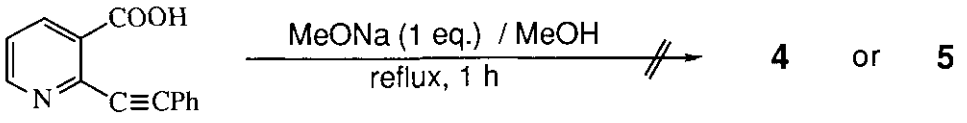


3 **4** 70 % **5** 11 %



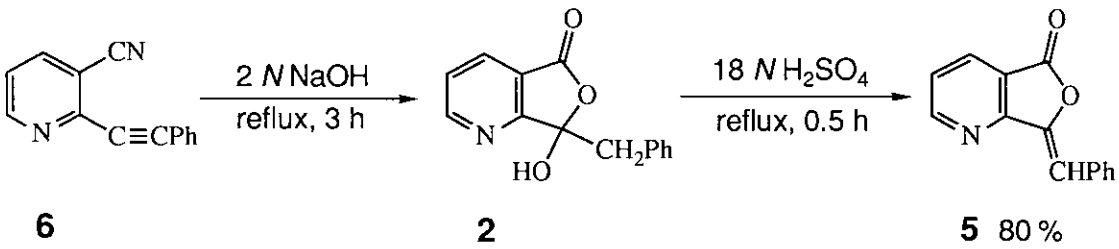
In this paper, we wish to report that the silica gel assisted cyclization of the pyridinecarboxylic acid (**3**) is an effective synthetic method of the furopyridine (**5**). A solution of carboxylic acid (**3**) and silica gel in ethyl acetate was heated at 60 °C for 1 day to afford the pyranopyridine (**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.



3 (1 eq.)

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

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7. The obtained bicyclic pyridines gave satisfactory spectral and analytical data (See reference 2).
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