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# The Preparation of N-Alkyl-2(1H)-pyridones by the Reaction of Amines with a Derivative of 3-(2-pyridyl)propane-1,2-diol

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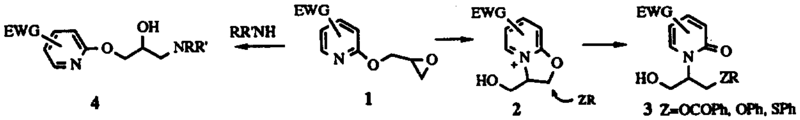
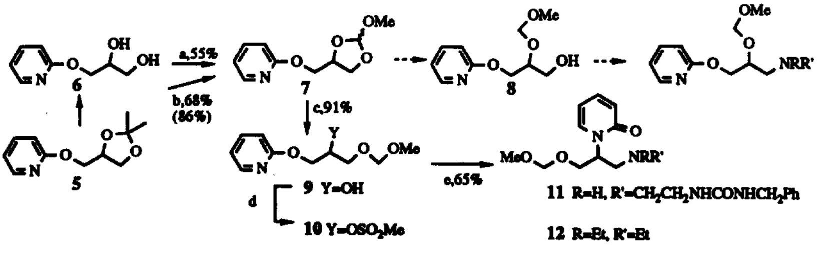
***Abstract:*** The reduction of the 2-pyridyl orthoester derivative 7 with DIBAL gives exclusively the secondary alcohol 9 in excellent yield. Mesylation of 9 followed by reaction with amines gives the unusual N-alkyl-2(1H)-pyridones 11 and 12.

Recently a new preparation of N-alkyl-2(1H)-pyridones (3) has been reported which involved a novel reaction of benzoic acid, phenol and thiophenol with 2-glycidoxy-pyridines (1) bearing electron withdrawing groups [1]. The mechanism proposed involves protonation of the oxygen of the epoxide ring followed by intramolecular ring opening by the pyridine nitrogen to give the intermediate 2 which goes on to react with the conjugate base of the acid, phenol or thiophenol[2]. This reaction is in stark contrast to the reaction of 2-glycidoxypyridines with amines which would be expected to give oxypropanolamines (4) (for example see note 3).



As part of a programme to develop new drugs for the treatment of congestive heart failure we were interested in preparing 2-pyridyloxypropanolamines lacking electron withdrawing groups. Synthesis from the unsubstituted 2-glycidoxypyridine is not possible because of the instability of that compound and consequently we investigated an alternative approach[3]. The results we obtained complement the research described above[1].



a: 2equ. TMOF, 1.1equ. TFA, $CH_2Cl_2$, RT b: 8equ. TMOF, 2.4equ. TFA, 4.5equ. MeOH, THF, reflux c: 3equ. DIBAL in hex., -78 to 0°C, $CH_2Cl_2$ d: $MeSO_2Cl$, $Et_3N$, THF e: 1.2equ. amine in 1vol. DMF, 3equ. $Et_3N$, 19vol. THF, reflux

We envisaged that the cyclic orthoester **7** could be selectively reduced to the primary alcohol **8**, using the methods described by Yamamoto[4], subsequently activated by mesylation and converted to a 2-pyridyloxypropanolamine by condensation with an amine. The orthoesters **7** were prepared as a pair of diastereoisomers either by reaction of the diol (**6**) with trimethyl orthoformate and trifluoroacetic acid or better, by exchange of the 1,3-dioxolane (**5**) with trimethylorthoformate in THF with methanol and trifluoroacetic acid as catalysts[5]. Reduction of **7** with DIBAL gave exclusively the secondary alcohol **9** in 91% yield, rather than the primary alcohol **8**[6]. This is presumed to have arisen from chelation rather than steric control. Mesylation of **9** to give **10** followed by reaction with the primary amine gave the unusual *N*-alkyl-2(1*H*)-pyridone **11** in 65% yield. It is proposed that **11** is formed via an intermediate analogous to **2**. Initial studies showed that the MOM group could be removed by treatment with trimethylsilyl bromide[7]. The product **12** derived from a secondary amine could be prepared similarly.

It is believed that these results point the way to a general route for preparing this type of *N*-alkyl-2(1*H*)-pyridone lacking electron withdrawing groups. It is not known whether the scope of the chemistry can be extended to include the reaction of **10** with carboxylic acids, phenols or thiophenols, or their conjugate bases. The acetonide **5** and diol **6** can be prepared in optically pure form[8] and it would be of great interest to investigate the fate of the stereochemistry during the sequence of reactions and in particular during the course of the O-to-N migration. In presenting these results we throw open these questions to the scientific community.

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**References and Notes:**

1. Schmidhauser J.C. and Longley K.L., *Tetrahedron Lett.*, **1991**, 32, 7155-8.
2. Intramolecular assistance from pyridyl nitrogen has also been demonstrated for the reaction of 4-(2-pyridyl)thiomethyl-1,3-dioxane with Grignard reagents. Marot C., Philipp C., and Rollin P., *Tetrahedron Lett.*, **1992**, 33, 4575-8.
3. 5-Chloro-2-glycidoxypyridine (cf.**1**), which is a stable, crystalline solid, reacts with amines to give oxypropanolamines and where appropriate the chlorine can be removed by hydrogenation.
4. Takasu M., Naruse Y. and Yamamoto H., *Tetrahedron Lett.*, **1988**, 29, 1947-50.
5. The two diastereoisomers of **7** were separated for the purposes of analysis, but otherwise used as a mixture. Full analytical data were obtained for all reported products.
6. The position of the free hydroxyl group was proved by derivatization with trichloroacetyl- isocyanate.
7. Hanessian S., Delorme D. and Dufresne Y., *Tetrahedron Lett.*, **1984**, 25, 2515.
8. Barlow J.J., Block M.H., Hudson J.A., Leach A., Longridge J.L., Main B.G. and Nicholson S., *J. Org. Chem.*, **1992**, 57, 5158-62.

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