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A New Preparation of N-Alkyl-2(1H)-pyridones from 2-Glycidoxypyridines

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Key Words: pyridone; N-alkyl-2(1H)-pyridone; nucleoside base analogue; pyridine; oxazolinium ion

Abstract: N-Alkyl-2(1H)-pyridones are prepared in high yield by the reaction of 2-glycidoxypyridines with carboxylic acids, phenols or thiophenols. These reactions proceed through an oxazolinium ion intermediate, which reacts with the acid counter ion to give the ultimate products.

The preparation of nucleoside base analogues is an active research area since members of this class of compounds show antiviral activity[1] and are used in DNA replication studies[2]. In connection with our work in this area, we required a series of functionalized N-alkyl-2(1H)-pyridones. Previous reported methods for preparing these compounds include N-alkylation of pyridones[3], oxidation of N-alkylpyridinium salts[4] and organometallic coupling of alkynes with isocyanates[5] or phosphinimines[6]. The applicability of several of these methods is limited by required harsh conditions or incompatibility with desired pyridone substitution patterns. In this Letter, we report a novel preparation of N-alkyl-2(1H)-pyridones from reaction of 2-glycidoxypyridines and various electrophiles. This reaction proceeds with good to excellent yield, and gives products with set regiospecificity of pyridone ring substituents as well as a functionalized N-alkyl substituent which is well suited for further synthetic transformations.

Glycidoxypyridines are prepared in modest yield (20-50% yield) by nucleophilic displacement of chlorine in the appropriate chloropyridine precursors by glycidol[7]. This reaction occurs only when the pyridine is substituted by strongly electron withdrawing groups. The effect of these groups is twofold: they activate the

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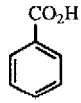
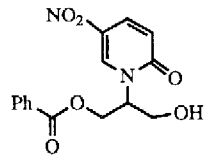
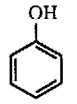
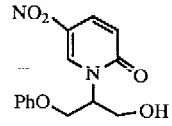
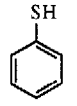
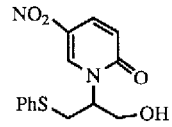
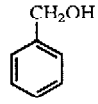
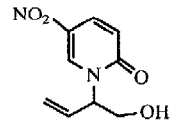
ring towards nucleophilic attack and lower the basicity of the pyridine nitrogen, thereby slowing the competing polymerization of glycidol. For example, 2-glycidoxy-5-nitropyridine **1** is prepared as a colorless crystalline solid (mp = 72.5-74.0 °C) in 40% yield from the chloronitropyridine (1.25 eq. glycidol, 1.5 eq. 50% aq. NaOH, 0.05 eq. Adogen® 464, toluene, 60°C, 2 h).

The reactivity of glycidoxypyridine **1** toward a number of reagents (5 eq. reagent, toluene, reflux) was explored (Table 1). Reaction with benzoic acid proceeds at a very fast rate ($t_{1/2}$ = 8 min.) to give pyridone product **2**. This reaction proceeds with O-to-N migration of the glycidyl-derived group, giving a product where the 3-carbon fragment is attached to the amide nitrogen at the secondary center with the two primary carbons

differentiated as an alcohol and benzoate ester. Weakly acidic phenol and thiophenol react with **1** at a slower rate than does benzoic acid. However, the products from their reactions (**3** and **4**, respectively) are structurally analogous, except that the N-alkyl fragment is substituted by a phenyl ether or phenyl thioether group instead of the benzoate ester.

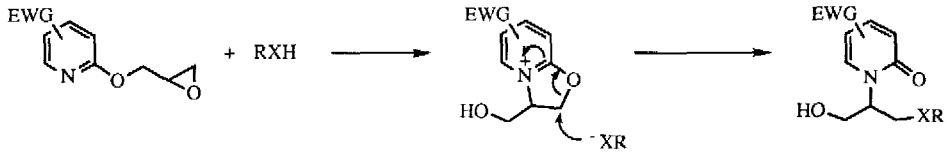
Table 1. Reactions of Glycidoxypyridine **1**.

Coreactant	Reaction Time (h)	Product (Nu.)		% Yield
	1		(**2**)	92
	24		(**3**)	86
	24		(**4**)	68
	72		(**5**)	50
None	72	" "	(**5**)	45

Reaction of **1** and benzyl alcohol gives, in addition to an intractable brick-red polymer, a pyridone whose spectral properties are consistent with structure **5**. The extremely slow rate at which **5** is formed, as well as the absence of the benzyl fragment in the product structure suggests that this reaction is different from those involving the more acidic reagents. Indeed, refluxing **1** in toluene gives the same product at a similar rate. Therefore, formation of **5** is a simple thermal process.

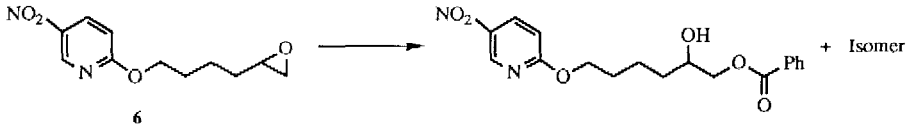
Spectral and chemical analyses support the N-alkyl-2(1H)-pyridone structures of **2-5**. Using **2** as an example, a strong signal at 1682 cm^{-1} in the infrared spectrum is at a frequency characteristic of the carbonyl stretch in a dienone. Further evidence for the disruption of the pyridine ring aromaticity is found in the ^1H NMR spectrum, where the ring proton signals are shifted upfield by 0.27 ppm (C3), 0.25 ppm (C4) and 0.17 ppm (C6) for **2** relative to **1**. Methanolysis (MeOH, sat. K_2CO_3) of **2** gives methyl benzoate and the expected symmetric diol.

The products from reactions of 2-glycidoxypyridines and organic acids, and the rates at which they are formed, are very different from those obtained in reactions of typical glycidyl ethers or esters. The unusual reactivity of 2-glycidoxypyridines may be explained by a mechanism where rapid protonation of the epoxide leads to the formation of an oxazolinium ion. This intermediate then reacts with the acid counter ion to give the



ultimate product. Therefore, the reactivity of the glycidoxypyridines is a consequence of the close proximity of the epoxide and pyridine nitrogen groups, which allows facile formation of a 5-membered ring intermediate.

To illustrate the importance of spatial positioning of the epoxide and pyridine nitrogen groups, we prepared hexoxyepoxypyridine **6** by reaction of 2-chloro-5-nitropyridine and hex-5-en-1-ol followed by MCPBA oxidation. Reaction of this extended epoxide with benzoic acid under the standard conditions is much



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slower than in the glycidoxy examples ($t_{1/2}$ = 4200 min.). Furthermore, the products of this reaction are a pair of isomeric pyridine ester-alcohols rather than a pyridone. If the reaction of **6** and benzoic acid were to proceed through a cyclic intermediate, it would be an eight-membered ring. This is apparently disfavored, since the reactivity of epoxide **6** is more typical of an isolated glycidoxyether or ester. For comparison, the reaction of glycidylnaphthyl ether and benzoic acid under the conditions used in this study is slow ($t_{1/2}$ = 15300 min.) and gives a mixture of isomeric ester alcohols from simple epoxide opening.

The generality of this method was explored by reacting a number of different glycidoxypyridines with benzoic acid (Table 2). In these examples, the reactions were complete within 2 h and gave the expected pyridones as the sole products in 75-90% yield.

While the preparation of glycidoxypyridines has not been optimized at this point, the simplicity, mild conditions and high yields of their reactions with organic acids provides a useful method to prepare certain pyridones. Furthermore, the presence of a highly functionalized N-alkyl substituent in the product is well suited for elaboration of other structures, for example carbohydrates. Further study of the usefulness of this method in the preparation of nucleoside intermediates, including the investigation of reactions of other glycidoxy azines, is in progress.

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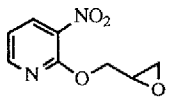
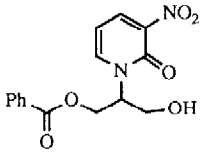
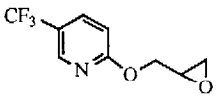
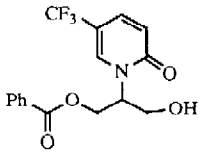
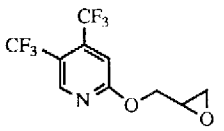
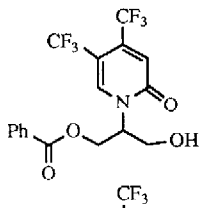
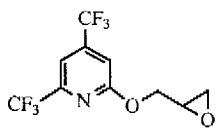
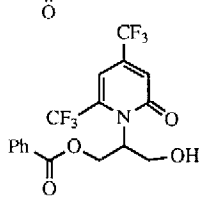
Table 2. Reactions of Glycidoxypyridines with Benzoic Acid.

Reactant	Product	% Yield
		75
		85
		90
		85

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