A Facile and Practical N-formylation of Aminoalcohol: For the Synthesis of 2-substituted 2-Oxazolines and 5,6-Dihydro-4H-1,3-Oxazines

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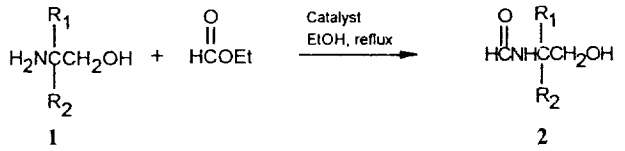
We have been interested in N-formylation of various aminoalcohols, in order to synthesize 2-substituted 2-oxazolines and 1,3-oxazines.[1,2] N-formylation reaction has been reported as a methodology for the preparation of amides from α-amino acids and amines.[3-5] Its application to aminoalcohols was not well documented in the literature. N-formylation of aminoalcohol **1a, b** with ethyl formate in ethanol at 80℃, proceeded to form N-(hydroxyalkyl) formamide **2a, b** very slowly and incompletely. In order to prepare a large amount of N-formyl aminoalcohol, we investigated to develop a facile and practical synthetic route by addition of a catalyst (Scheme 1).

Addition of a catalytic amount of sodium was remarkably accelerated reaction. It took less than 2 hrs to complete the reaction as compared to more than 24 hrs without catalyst.[6] Under this condition, the starting material was also converted completely and gave rise to near quantitative yield. Since chromatographic isolation of products was not necessary, preparation time was shortened significantly.

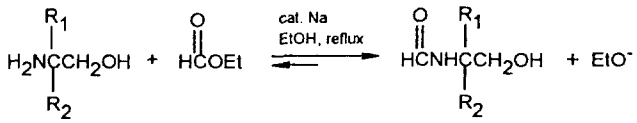
We assumed that ethoxide formed by sodium kept the reaction in basic medium to accelerate attack of a lone pair of nitrogen to a carbonyl of ethyl formate and then shifted the equilibrium to formamide. Exact reaction mechanism for effect of addition of sodium is under investigation (Scheme 2).

A large amount of N-formyl aminoalcohol in hand, N-(2-hydroxyalkyl) formamide was further converted to 2-unsubstituted 2-oxazoline by modifying Wenker's methods.[7] Chlori-

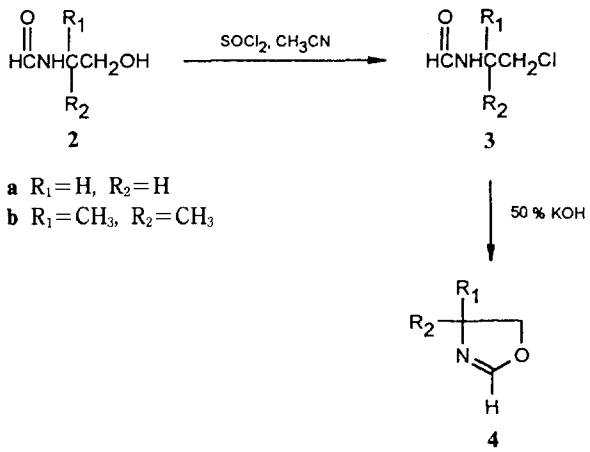


a $R_1=H$, $R_2=H$
b $R_1=CH_3$, $R_2=CH_3$

Scheme 1.



Scheme 2.



Scheme 3.

nation of N-(2-hydroxyalkyl) formamide **2a, b** with thionyl chloride in acetonitrile gave N-(2-chloroalkyl) formamide **3a, b** in 72% yields. The target compound **4a, b** were obtained by cyclization of N-(2-chloroalkyl) formamide **3a, b** in 50% KOH solution in 65% yield (Scheme 3).[8]

In conclusion, we have shown that N-formylation of aminoalcohols in the presence of catalytic amounts of sodium proceeded completely. These procedure could be extended to N-formylation of other interesting nitrogen compounds. Several application of this methodology are in progress.

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6. Typical procedure: Sodium metal (77.0 mg, 3.33 mmol, 0.05 equiv) was dissolved in ethanol at 0℃ under nitrogen in a two necked flask equipped with a reflux condensor. To this solution was added 3-amino-1-propanol (5.00 g, 66.6 mmol, 1.00 equiv), and then stirred for 30 min at room temperature. Ethyl formate (7.39 g, 99.9 mmol, 1.50 equiv) was added dropwise to the above mixture at 0℃. After the addition was complete, the mixture was heated at reflux until TLC showed no starting material. The mixture was filtered through silica gel pad, and concentrated under reduced pressure to afford N-formyl aminoalcohol as a colorless oil in quantitative yields.
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8. All compounds were fully characterized by spectroscopic methods. All yields refer to isolated.