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IMPROVED PROCEDURES FOR PREPARATION OF 2-PYRIDONES AND 2-HYDROXYMETHYLPYRIDINES FROM PYRIDINE N-OXIDES

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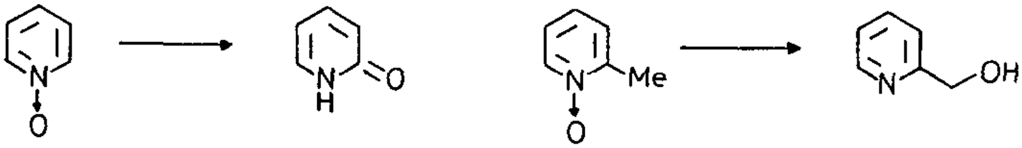
Abstract ——— 2-Pyridones and 2-hydroxymethylpyridines were prepared from pyridine N-oxides by treatment with trifluoroacetic anhydride in dimethylformamide. The reaction proceeds at room temperature in satisfactory yields.

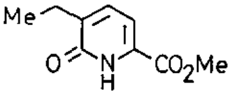
In the course of synthetic studies on acromelic acid A and B, the neurotoxins from a poisonous mushroom[1], we needed to synthesize 6-carboxy-2-pyridones from the corresponding pyridine N-oxides. Conversion of pyridine N-oxides into 2-pyridones is a well established reaction developed by Ochiai and his co-workers, and has been frequently used in heterocyclic chemistry.[2] However, studies showed that application to picolinic acid derivatives gave poor results.[3] We report here improved procedures in which the reaction proceeds rapidly under mild conditions to give 2-pyridones and 2-hydroxymethylpyridines from the corresponding pyridine N-oxides in satisfactory yields.[4]



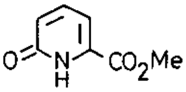
We first explored the reaction of 2-carbomethoxy-5-ethylpyridine N-oxide[5] as a model substrate, with a variety of acid anhydrides other than acetic anhydride and found that trifluoroacetic anhydride (TFAA) gave a promising result, that is, the reaction proceeded at room temperature to afford 6-carbomethoxy-3-ethyl-2-pyridone

1 in ca. 15% yield. To improve the yield, the solvent effect was next examined. Although the solvents such as CH_2Cl_2, THF and CH_3CN had no favorable effect, a polar aprotic solvent dimethylformamide (DMF)[6] markedly increased the yield up to 75%. Thus, the use of 10 equiv of TFAA in DMF at room temperature for 16 h was most satisfactory. Exposure of some other pyridine N-oxides to this improved procedure furnished the pyridones 2-5[7] in yields shown in parentheses (Fig. 1). Under the above conditions the protective groups MEM and BOC were not affected. Therefore, the procedure seems to be useful for the synthesis of complex natural products.[8]

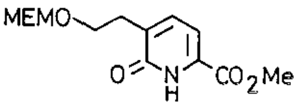
Figure 1



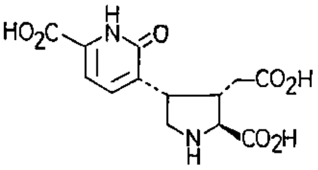
1 (75%)



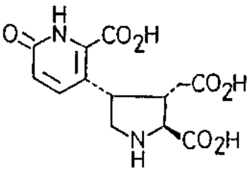
2 (55%)



3 (70%)



4 (68%)



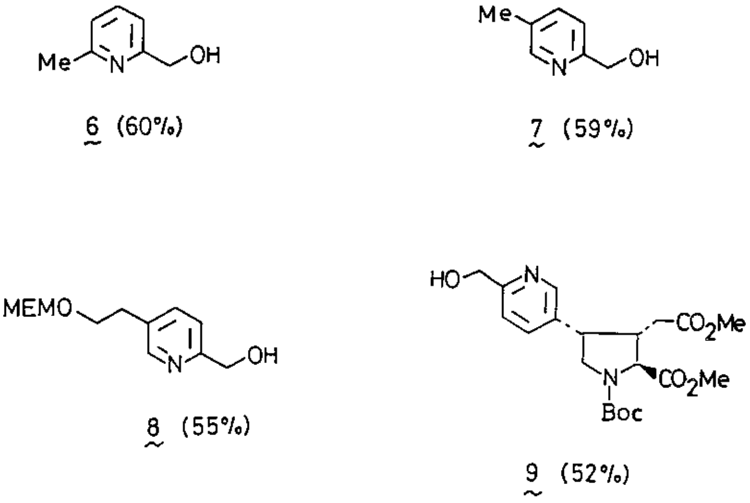
5 (62%)

The above procedure successfully was applicable also to 2-picoline derivatives, giving 2-hydroxymethylpyridines through simple operations.[9] The results are summarized in Figure. 2 (6-9[7]).

A typical experimental procedure is as follow:

To a solution of 2-carbomethoxy-5-ethylpyridine N-oxide (500 mg) in DMF (10 ml) was added TFAA (3.9 ml, 10 equiv) and the mixture was kept at room temperature for

Figure 2



6 (60%)

7 (59%)

8 (55%)

9 (52%)

16 h. After the excess TFAA was evaporated under reduced pressure, the mixture was poured into water and extracted with benzene. The combined extracts were washed twice with brine, dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was purified by silica gel column chromatography (12 g, 1% cMeOH/$CHCl_3$) to furnish 5-carbomethoxy-3-ethyl-2-pyridone as white crystals (375 mg, 75%), mp 97-98 °C.

Further Scope and limitation of this improved procedure are now under investigation.[10]

REFERENCES AND NOTES

1. K. Konno, H. Shirahama and T. Matsumoto, Tetrahedron Lett., 1983, **24**, 939.
2. E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967.
3. V. Boekelheide and W. L. Lehn, J. Org. Chem., 1961, **26**, 428.
4. A part of this work was presented at the 17th Congress of Heterocyclic Chemistry, in Sapporo, Japan, 1985, August 28, Abstr., p. 133.
5. This compound was prepared from 5-ethyl-2-methylpyridine through (1) SeO_2/Py, (2) CH_2N_2 and (3) mCPBA in high yield.
6. The polar aprotic solvents such as HMPA (hexamethylphosphoramide), DMI (1, 3-

dimethyl-2-imidazolidinone) and DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) gave comparable results.

7. All the data of these compounds were consistant with the assigned structures or those reported in literature.
8. K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama and T. Matsumoto, *Tetrahedron Lett.*, 1986, **27**, 607.
9. Recently a comparable work was presented: A. McKillop and M. K. Bhagroth, *Heterocycles*, 1985, **23**, 1697.
10. For example, quinoline 1-oxide gave carbostyril in 60% yield with TFAA/DMF. The best yield under the classical conditions was 32.4%; K. Funakoshi, Y. Kuchino, H. Shigyo, H. Sonoda and M. Hamana, *Chem. Pharm. Bull.*, 1976, **24**, 2356.

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