2. S. Gronowitz and J. Roe, Acta Chem. Scand., 19, 1741(1965), and J. D. Davenport, R. E. Hackler, and H. E. Taylor, British Patent 1,218,623; Chem. Abstr., 75, 15186h(1971).
3. T. J. Kress, J. Org. Chem., 44, 2081(1979).
4. A portion of this work has been reported, T. J. Kress and E. F. Szymanski, U. S. Patent 4, 252,955(1981); Chem. Abstr., 94, 192368m(1981).
5. Org. Synthesis, Coll. Vol. 4, 688(1963).
6. Y. Hachilhama, T. Shono, and S. Ikeda, J. Org. Chem. 29, 1371(1964).
7. B. Lythgoe and L. Rayner, J. Chem Soc., 2323(1951).

NEW APPLICATIONS OF MONONUCLEAR HETEROCYCLIC REARRANGEMENTS (MHR's) IN ORGANIC SYNTHESIS

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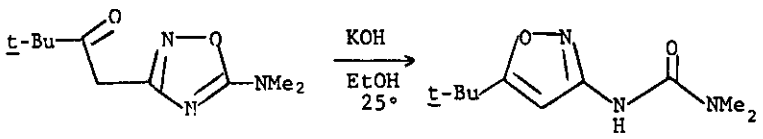
Mononuclear heterocyclic rearrangements[1] represent a class of azole/azole interconversions first systematized by Boulton and Katritzky[2]. Interest in the synthesis of LY 108887 prompted our consideration of a scarcely documented version of this rearrangement. Thus, reaction of methyl pivalate with 3-methyl-5-dimethylamino-1,2,4-oxadiazole in the presence of lithium diisopropylamide (LDA) at low temperature, followed by quench with aqueous acid at 0° gave LY 156544 in high yield. Treatment of this compound with ethanolic potassium hydroxide gave LY 108887 in quantitative yield.



LY 156544 LY 108887

Further examples of this condensation/rearrangement sequence and extensions to other heterocyclic ring systems are discussed.

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1. Recent review: M. Ruccia, N. Vivona, and D. Spinelli, Adv. Het. Chem., 29, 141 (1981).

2. A. J. Boulton, A. R. Katritzky, and A. M. Hamid, J. Chem. Soc. C, 2005 (1967).

6-SUBSTITUTED NICOTINIC ACIDS FROM 2-METHYL-5-ETHYLPYRIDINE

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Work was done by Dr. Daniel Quarroz, Lonza AG, 3930 Visp, Switzerland

In our continuing exploration or the chemistry of isocinchomeronic

acid, made by oxidation of 2-methyl-5-ethylpyridine, we observed a novel transformation of this pyridine dicarboxylic acid to variously 6-substituted nicotinic acids.

When isocinchomeronic acid-N-oxide was reacted with acetic anhydride/triethylamine in methylenechloride 6-chloronicotinic acid was obtained in 50% yield, the chlorine originating from the solvent. 6-Hydroxynicotinic acid was identified as a side product in 40% yield. This unusual and unexpected chlorination with methylenechloride was also tried successfully on other pyridine carboxylic acids bearing a carboxyl group in the 2 position to the nitrogen. The carboxyl group was invariably replaced by chlorine.

When in the system isocinchomeronic acid-N-oxide/acetic anhydride/triethylamine the methylenechloride was replaced by another solvent, a radical of this solvent was found as substituent in the 2 position. In acetonitrile as solvent 6-aminonicotinic acid was isolated in 80% yield. In ethylacetate 6-hydroxynicotinic acid was formed in 80-86% yield. The benezene- and toluene-radical was also introduced into the 2 position.

We are continuing to study the scope of this reaction, which gives easy access to 6-substituted nicotinic acids hitherto available only on very cumbersome routes.

Annelated Derivatives of 2,2'-Bipyridine and 2,2'-Bi(1,8)naphthyridine

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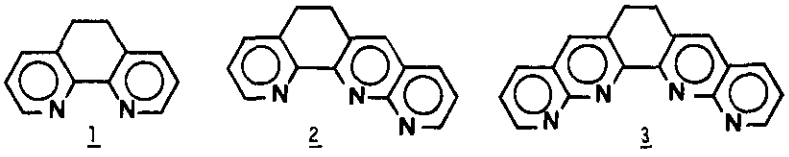
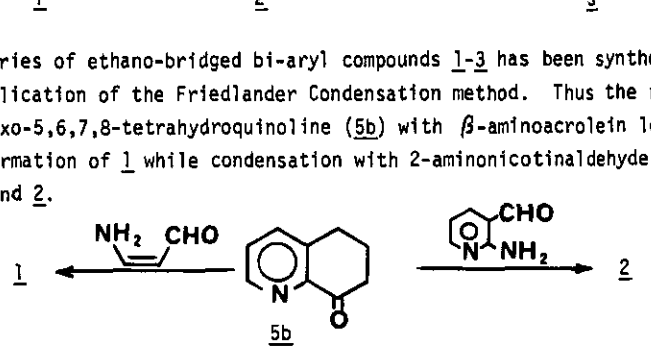


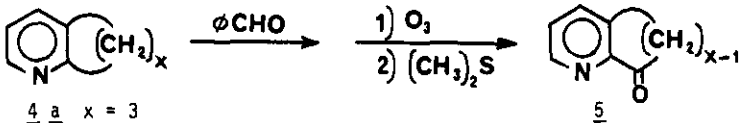
1 2 3

The series of ethano-bridged bi-aryl compounds 1-3 has been synthesized by application of the Friedlander Condensation method. Thus the reaction of 8-oxo-5,6,7,8-tetrahydroquinoline (5b) with β-aminoacrolein leads to the formation of 1 while condensation with 2-aminonicotinaldehyde gives compound 2.



5b

The 2-oxocycloalkenopyridines (5 a-c) are readily prepared by a two step route from the corresponding commercially available cycloalkenopyridines.



4 a x = 3
b x = 4
c x = 5

5