

# Preparation of 4-Aryl- and 4-Heteroaryl-pyridines: Regiospecific Nucleophilic Attack $\gamma$ to a Quaternary Nitrogen Atom

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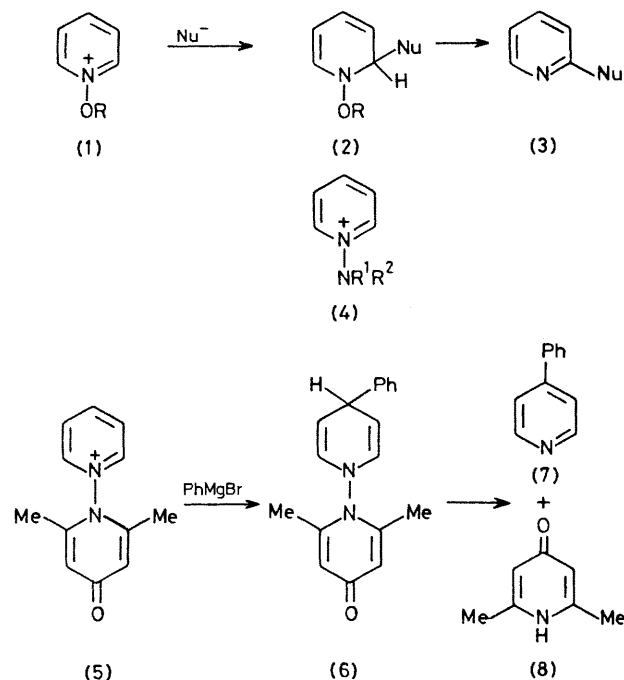
**Summary** 1-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium cation reacts with aryl and heteroaryl Grignard reagents to give regiospecifically the corresponding 4-arylpiperidines.

NUCLEOPHILIC substitution reactions at an unactivated pyridine ring generally need or are facilitated by quaternisation or *N*-oxide formation. Previously reported examples of nucleophilic attack on such derivatives have occurred either predominantly  $\alpha$  to the cationic nitrogen atom or give a mixture of comparable amounts of  $\alpha$  and  $\gamma$  products. We now describe our initial success in providing a new and generally applicable method to achieve efficiently and regiospecifically such  $\gamma$  substitution.

Nucleophiles react with quaternary derivatives of *N*-oxides [cf. (1)] to give [via the adduct (2)] a 2-substituted pyridine (3) (sometimes mixed with the 4-substituted analogue);<sup>1</sup> some corresponding reactions occur for *N*-amino derivatives (4).<sup>2</sup> Such *N*-substituents first activate the ring to nucleophilic attack and are then eliminated with simultaneous rearomatization. The novel factor of our own proposed work is that the *N*-substituent, while retaining the above functions, is constructed so as to cause steric shielding of the  $\alpha$  positions of the ring, thus directing the nucleophile into the position  $\gamma$  to the quaternary nitrogen. Such a substituent is 2,6-dimethyl-4-oxopyridin-1-yl; 1-aminopyridinium (readily available from pyridine) is converted in high yield by dehydroacetic acid into the 1-(4-oxopyridinio)pyridinium cation (5), and analogues of (5) are readily available from the parent heterocycles.<sup>3,4</sup>

This synthetic strategy has now been applied to the preparation of a series of 4-aryl- and 4-heteroaryl-pyridines.<sup>4</sup> In the prototype reaction, the oxopyridiniopyridinium (5) is treated with phenylmagnesium bromide. The initial product is the addition compound (6) which can be isolated, but which is advantageously cleaved *in situ* to a readily separated mixture of 2,6-dimethyl-4-pyridone (8) and 4-phenylpyridine (7) (68%, overall yield from pyridine 45%). No 2-phenylpyridine was detected. Use of the appropriate aryl Grignard reagent gives good yields of 4-*p*-methylphenyl-, 4-*p*-chlorophenyl-, 4-*p*-bromophenyl-, 4-*m*-methoxyphenyl-, 4-*o*-methylphenyl-, 4-*p*-methoxyphenyl-, and 4-(2-thienyl)-pyridine.

The pyridine ring may itself initially carry substituents: thus we have prepared 2-methyl-4-phenylpyridine and



3-methyl-4-phenylpyridine in good yields from 2- and 3-picoline respectively.

Previously the preparation of 4-arylpiperidines has involved either a multistage ring synthesis from difficultly accessible substituted  $\alpha$ -methylstyrenes as starting materials,<sup>5</sup> or, more usually, substitution of pyridine by free radicals from diazonium cations.<sup>6</sup> Such radical substitutions produce in poor to moderate yields a difficultly separable mixture of the 2-, 3-, and 4-substituted pyridines, of which the last is a minor component.<sup>6</sup>

Our new method has wide potential applicability. We have already shown<sup>7</sup> that cyanide ion adds regiospecifically to the 4-position of (5). We plan to test its limits in respect to (a) the range of heterocyclic rings and nucleophiles, (b) which substituents can be tolerated in the initial ring, and (c) whether 2,6-dimethyl-4-oxopyridin-1-yl is the optimum *N*-substituent.

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<sup>4</sup> A. R. Katritzky, H. Beltrami, and M. P. Sammes, unpublished work.

<sup>5</sup> C. J. Schmidle and R. C. Mansfield, *J. Amer. Chem. Soc.*, 1956, **78**, 1702.

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<sup>7</sup> C. W. F. Leung, M. P. Sammes, and A. R. Katritzky, *J.C.S. Perkin I*, in the press.