Preparation of 4-Aryl- and 4-Heteroaryl-pyridines: Regiospecific Nucleophilic Attack γ to a Quaternary Nitrogen Atom

By ALAN R. KATRITZKY* and HECTOR BELTRAMI
(*School of Chemical Sciences, University of East Anglia, Norwich* NR4 7TJ)
and MICHAEL P. SAMMES
(*Department of Chemistry, University of Hong Kong, Hong Kong*)

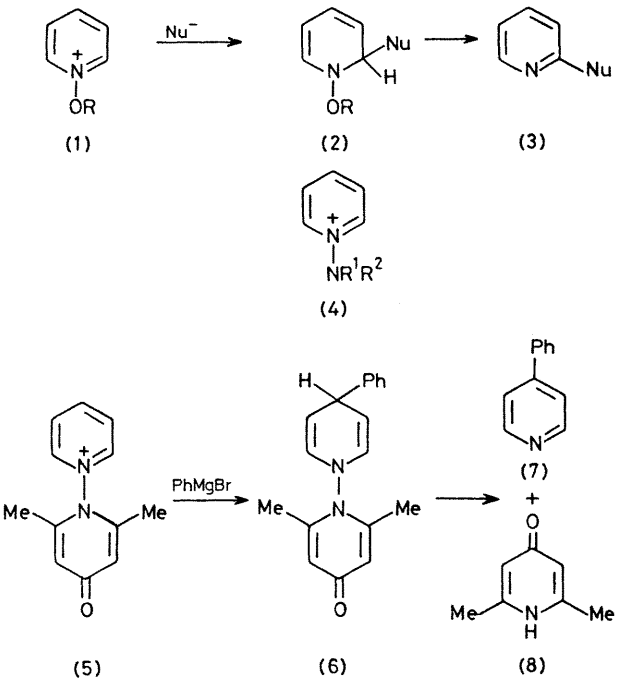
Summary 1-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium cation reacts with aryl and heteroaryl Grignard reagents to give regiospecifically the corresponding 4-arylpyridines.

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 α to the cationic nitrogen atom *or* give a mixture of comparable amounts of α and γ products. We now describe our initial success in providing a new and generally applicable method to achieve efficiently and regiospecifically such γ 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);[1] some corresponding reactions occur for *N*-amino-derivatives (**4**).[2] 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 α positions of the ring, thus directing the nucleophile into the position γ 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.[3,4]

This synthetic strategy has now been applied to the preparation of a series of 4-aryl- and 4-heteroaryl-pyridines.[4] 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.



(1) (2) (3) (4) (5) (6) (7) (8)

Previously the preparation of 4-arylpyridines has involved either a multistage ring synthesis from difficultly accessible substituted α-methylstyrenes as starting materials,[5] or, more usually, substitution of pyridine by free radicals from diazonium cations.[6] 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.[6]

Our new method has wide potential applicability. We have already shown[7] 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.

(*Received, 2nd November* 1978; *Com.* 1170.)

[1] For a review, see A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, London, 1971.
[2] T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 780; T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *ibid.*, 1966, **14**, 506; T. Okamoto, M. Hirobe, and T. Yamazaki, *ibid.*, p. 512; T. Okamoto, M. Hirobe, and A. Ohsawa, *ibid.*, p. 518.
[3] A. R. Katritzky and M. P. Sammes, *J.C.S. Chem. Comm.*, 1975, 247; M. P. Sammes, H. K. Wah, and A. R. Katritzky, *J.C.S. Perkin I*, 1977, 327.
[4] A. R. Katritzky, H. Beltrami, and M. P. Sammes, unpublished work.
[5] C. J. Schmidle and R. C. Mansfield, *J. Amer. Chem. Soc.*, 1956, **78**, 1702.
[6] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 1940, 349; E. C. Butterworth, I. M. Heilbron, and D. H. Hey, *ibid.*, p. 355.
[7] C. W. F. Leung, M. P. Sammes, and A. R. Katritzky, *J.C.S. Perkin I*, in the press.