A New Synthesis of 2,5-Disubstituted Pyridines

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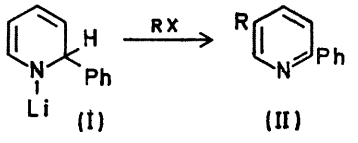
Summary 2,5-Disubstituted pyridines have been obtained in one step by the addition of organic halides to organolithium–pyridine reaction intermediates.

THE direct alkylation or arylation at the 3- or 5-position of the pyridine ring is difficult;[1] thus, alkylation and arylation of pyridine by organolithium compounds or Grignard reagents give 2- or 4-substituted pyridines rather than the 3-substituted derivatives. Free-radical substitution reactions, on the other hand, give a mixture of all three isomers but the 3-isomer is usually the minor component. Also, the latter method cannot be used to arylate or alkylate arylpyridines because the benzene ring rather than the pyridine is attacked. Finally, there has been no report on the synthesis of 2,5-disubstituted pyridines based on the intermediates isolated from the reactions of pyridine with organolithium compound.

We recently[2] isolated the intermediate, 1-lithio-2-phenyl-1,2-dihydropyridine (I) formed in the reaction of phenyllithium with pyridine; when a solution of this intermediate



(I) (II)

(IIa) R = Me
(IIb) R = Ph
(IIc) R = PhCH$_2$
(IId) R = Br

(I) in tetrahydrofuran and at 0° was treated with methyl iodide, 5-methyl-2-phenylpyridine (IIa) was obtained (34% yield). Similarly, when (I) was treated with iodobenzene, benzyl chloride, or bromine, 2,5-diphenylpyridine (IIb), 5-benzyl-2-phenylpyridine (IIc), and 5-bromo-2-phenylpyridine (IId), respectively, were obtained. When the above electrophilic reagents were added to an equimolar mixture of phenyl-lithium and pyridine [rather than to the isolated intermediate (I)], the corresponding 2,5-disubstituted pyridines could be detected but the reaction mixture contained several other products. Except for 5-bromo-2-phenylpyridines,† all the above compounds were identical with authentic samples prepared by unambiguous methods.[3–6] After these reactions were carried out, we found a report[7] that a similar *in situ* reaction but using triphenylmethyl chloride also gave small amounts of 2-phenyl-5-triphenylmethylpyridine. Although the *in situ* reactions are a one-step process, we recommend the former procedure which uses the isolated intermediate, because the product obtained is clean and uncontaminated with side-products.

Although no attempt was made to optimize the reaction conditions for maximum yields, the yields obtained by the above procedures exceeded those obtained from previously reported methods.[3–6] For example, the simplest procedure[3] to prepare 5-methyl-2-phenylpyridine gave a 2% yield; the yield by the above procedure was 45%. Also, the old methods often require several steps; thus, the preparation of 2,5-diphenylpyridine from 3-bromopyridine involved five instead of one synthetic steps.[4,5]

The C-5 alkylation was not restricted to the intermediates formed from phenyl-lithium and pyridine because the intermediate from n-butyl-lithium and pyridine with methyl iodide gave 5-methyl-2-n-butylpyridine.

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† 5-Bromo-2-phenylpyridine has not been reported; its n.m.r. and mass spectra, and the elemental analysis were consistent with the assigned structure. We thank Professor Ronald D. Grigsby for the mass spectral analysis.

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