General Synthesis of 2,6-Dialkylpyridines

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Summary The reactions of pyridine with excess of alkyl-lithium compounds generally give excellent yields of 2,6-dialkylpyridines.

REACTIONS[1] of pyridine with alkyl-lithium reagents are an important source of 2-alkylpyridines. Some 2,6-dialkylpyridines have been prepared analogously from 2-alkylpyridines and alkyl-lithiums. Although a number of monoalkyl-, dialkyl-, and trialkyl-pyridines are at least theoretically possible in these reactions, only these single-step substitutions occurring α to the pyridine nitrogen have been reported.[1] We have found that, in general, the reaction of pyridine with an excess of an alkyl-lithium reagent gives in addition to the 2-alkylpyridine, the 4-alkyl-, 2,4-dialkyl-, and 2,6-dialkyl-pyridine. This reaction is significant in that under suitable conditions, it affords a convenient synthesis of either the 2-alkyl- or 2,6-dialkylpyridine in yields that are generally superior to those obtained by other methods.[2]

In order to obtain the 2-alkylpyridine in high yield an equivalent amount or preferably an excess of pyridine is required. These reactions are reasonably well documented.[1,2] The general procedure employed in this investigation for preparing 2,6-dialkylpyridines involves addition of pyridine in hexane to an excess of the alkyl-lithium reagent. When the alkyl-lithium was prepared in a solvent of lower b.p. than hexane, the solvent was distilled off after addition of the pyridine–hexane solution, and the resulting mixture was heated under reflux for 48 h. The reaction flask was cooled in an ice bath and the unchanged alkyl-lithium slowly decomposed by the addition of water. The residue obtained from the ether extract of the mixture was distilled and analysed by g.l.c. The results of our initial studies are summarized in the Table.

TABLE

	Yields[b] (%) of alkylpyridines[c]				
Alkyl-lithium[a]	2-	4-	2,4-di-	2,6-di-	2,4,6-tri-
EtLi		(traces)		90	
$\mathrm{Pr^{i}Li}$	9	15	4	51	
$\mathrm{Bu^{n}Li}$ ..		(traces)		89	
$\mathrm{Bu^{t}Li}$[d]	9	7	22	58	
$\mathrm{Bu^{t}Li}$[e]			1	5	80

[a] All reactions employed a 1:10 mol pyridine:RLi ratio. [b] Yields are calculated from g.l.c. analyses of weighed residues. [c] Alkylpyridines were identified by comparison of their i.r. and n.m.r. spectra with those of commercially purchased samples and/or comparison of derivative melting points with those reported in the literature. The products were generally obtained in 95% or greater purity by distillation. [d] Room temperature. [e] Refluxing heptane.

The reaction of pyridine with excess of t-butyl-lithium also gives the 2,4,6-trialkylpyridine although this product was not found in other reactions. The optimum yield of 2,6-di-t-butylpyridine was obtained by adding pyridine to an excess of t-butyl-lithium at −70 °C. The mixture was allowed to reach room temperature, stirred for 72 h, and worked up as previously described. When the same pyridine–t-butyl-lithium mixture was refluxed in heptane for 48 h, 2,4,6-tri-t-butylpyridine[3] was obtained in 80% yield.

Support of the Robert A. Welch Foundation is gratefully acknowledged.

(*Received, September 20th,* 1971; *Com.* 1638.)

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[1] K. Ziegler and H. Zieser, *Ber.*, 1930, **63**, 1847; H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, 1966, **88**, 986; J. C. van der Plas and J. J. den Hertog, *Rec. Trav. chim.*, 1962, **81**, 841.

[2] For a general survey see L. E. Tenanbaum in 'The Chemistry of Heterocyclic Compounds', Vol. 14, ed. E. Klingsberg, Interscience, New York, 1961, ch. V, p. 155 and references therein.

[3] K. Kimroth and W. Mack, *Angew. Chem., Internat. Edn.*, 1968, **7**, 460.