C-Alkylation of Aldehyde Enamines

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ONE of the most elegant procedures for the alkylation of ketones is the enamine synthesis devised by Stork and his co-workers.[1] The enamine method has several advantages over methods which involve the reactions of enolate anions. Not the least of these is that reaction occurs under conditions mild enough to be compatible with the presence in the enamine part of a variety of functional groups, thereby facilitating synthesis of polyfunctional molecules. Unfortunately attempts to extend this alkylation to enamines of aldehydes have met with little success, the products being those of *N*-alkylation and aldol condensation rather than *C*-alkylation.[2]

Following a study of factors influencing the alkylation of enamines, we now report that aldehyde enamines derived from n-butylisobutylamine can in fact be *C*-alkylated, often in good yield (see Table).

The success of these alkylations is due, at least in part, to the prevention of *N*-alkylation by the steric bulk of the alkyl groups attached to nitrogen, there being a good correlation between the yield of *C*-alkylation and the bulk of the alkyl groups on nitrogen.[3] Since aldehyde enamines of n-butyl isobutylamine are preparable in good yield by the usual methods,[4] their successful alkylation constitutes a useful extension of the enamine synthesis.

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TABLE

Aldehyde	Alkylating agent[a]	Yield of monoalkylated aldehyde (per cent)[b]
Valeraldehyde	methyl iodide	66
	ethyl iodide	78
	n-butyl iodide	25
Butyraldehyde	methyl iodide	58
	ethyl iodide	41
	n-butyl iodide	34
Isobutyraldehyde	methyl iodide	64
Phenylacetaldehyde	methyl iodide	80
	ethyl iodide	73

[a] Solvent was acetonitrile. Two moles of alkylating agent per mole of enamine were employed.

[b] Determined by gas-liquid phase chromatography. Products were identified either by isolation and comparison with authentic samples or by isolation, examination by n.m.r. spectroscopy, and preparation of solid derivatives.

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[2] E. Elkik, *Bull. Soc. chim. France*, 1960, 972; K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, 1961, **26**, 3576; G. Opitz and H. Mildenberger, *Annalen*, 1961, **649**, 26; G. Opitz, *ibid*,. 1961, **650**, 122.

[3] T. J. Curphey and Jennie Chao-yu Hung, unpublished work.

[4] C. Mannich and H. Davidson, *Chem. Ber.*, 1963, **69**, 2106; E. Benzing, *Angew. Chem.*, 1959, **71**, 521.