Alkylation of Bicyclic Imines with the Stork–Dowd Reagent System

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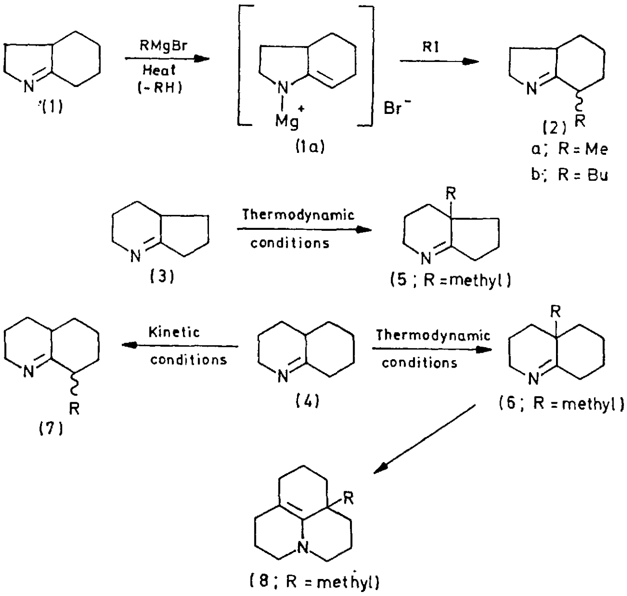
Summary The alkylation of selected bicyclic imines *via* the Stork–Dowd reagent system under equilibrating conditions is reported to give products predictable by thermodynamic principles and in contrast to kinetic results.



Stork and Dowd have demonstrated that aldehydes and ketones can be alkylated *via* the metalloenamines derived by treatment of the corresponding *N*-alkylimines with strong bases such as Grignard reagents.[1] The general reactions of such metalloenamines was later extended by Wittig for use in directed aldol condensations[2] and this latter sequence has been widely used in synthesis[3] where conventional aldol techniques either fail or give the alternate mode of condensation.

Recently, Stork and Benaim[4] have demonstrated that the monoalkylation of α,β-unsaturated ketones can selectively yield different products (under kinetic *versus* thermodynamic conditions).

We now report that the alkylation of several bicyclic imines under thermodynamic reaction conditions affords alkylated products which may be predicted by an extension of the Brown–Brewster–Schechter rule.[5] Alternatively,

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application of kinetic conditions offers the option of another mode of positional alkylation in certain cases.

$\Delta^{1,8}$-Hexahydroindole[6] (**1**) was refluxed (4—6 h) with a *slight* excess of isopropylmagnesium bromide in THF to form the equilibrated metalloenamine salt (**1a**), which when reacted with alkyl iodides gave the 7-substituted $\Delta^{1,8}$-hexahydroindoles (**2**) in distilled yields of 60—70%.‡§ Similar alkylation of $\Delta^{1,8}$-hexahydro-1-pyridene [6a,7] (**3**) and $\Delta^{1,9}$-octahydroquinoline[7,8] (**4**) with methyl iodide *via* the magnesium metalloenamine salts under equilibrating conditions gave only the angularly substituted cyclic imines, (**5**) and (**6**), in distilled yields of 59% and 58%, respectively.

The alkylation of (**4**) under thermodynamic conditions contrasts sharply with alkylation under kinetic conditions where substitution cleanly occurs in high yield at the 8-position of the octahydroquinoline.[9]

The selectivity with which the Stork–Dowd reagent system can be controlled for directing alkylations by choice of reaction conditions (kinetic *vs.* thermodynamic) is thus shown to offer greater versatility than earlier recognized. Additionally, the metalloenamines formed by the equilibrating conditions utilized in the three basic bicyclic imine systems employed here clearly demonstrates that the same thermodynamic principles[5] for olefin preference in alkylcyclohexene ⇌ alkylidenecyclohexane and alkylcyclopentene ⇌ alkylidenecyclopentane systems is valid for predicting the preferred metalloenamine and thus the thermodynamically favoured position of alkylation in such imine systems.¶

Finally, we wish to call attention to the application of these simple techniques for building angular alkyl substituents into the hydrojulolidine ring skeleton by repeating the metalloenamine formation on (**6**) and alkylating with 1-chloro-3-iodopropane under conditions so that both alkylation and ring closure occurs[9] with resultant formation of (**8**).

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‡ Alkylation of (**1**) afforded (**2a**) (picrate, m.p. 172—173·5, decomp.) in 66% yield whose n.m.r. spectrum indicated the presence of two isomers in a ratio of 4:1 by the presence of methyl doublets centred at δ 1·15 (major isomer) and 1·01 (minor isomer).

§ All new compounds gave correct elemental analysis (as picrates) and spectroscopic data.

¶ The applicability of the same thermodynamic preferences also appears to hold for similar heterocyclic enamine systems (*e.g.*, tertiary pyrrolines, tertiary piperideines, dehydroindolizidenes, and dehydroquinolizidines) from a study of their spectral properties.[10]

[1] G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, 1963, **85**, 2178.
[2] G. Wittig and H. Reiff, *Angew. Chem. Internat. Edn.*, 1968, **7**, 7: G. Wittig and H.-D. Frommeld, *Chem. Ber.*, 1964, **97**, 3548.
[3] For example, see G. Büchi and H. Wüest, *J. Org. Chem.*, 1969, **34**, 1122.
[4] G. Stork and J. Beniam, *J. Amer. Chem. Soc.*, 1971, **93**, 5938.
[5] H. C. Brown, J. H. Brewster, and H. Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.
[6] (a) E. F. Godfroi and L. H. Simanyi, *J. Org. Chem.*, 1962, **27**, 3882; (b) V. Boekelheide, M. Müller, J. Jack, T. Grossnickle, and M. Chang, *J. Amer. Chem. Soc.*, 1959, **81**, 3955; (c) B. Belleau, *Canad. J. Chem.*, 1957, **35**, 651.
[7] L. A. Cohen and B. Witkop, *J. Amer. Chem. Soc.*, 1955, **77**, 6595.
[8] R. F. Parcell, *J. Amer. Chem. Soc.*, 1959, **81**, 2596.
[9] D. A. Evans, *J. Amer. Chem. Soc.*, 1970, **92**, 7593; kinetic alkylation of (**4**) *via* the lithium metalloenamine with 1-chloro-3-iodopropane at −50 °C afforded [(**7**) R = $-CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}Cl$)] which was subsequently cyclized by heating to form the hydrojulolidine [(**8**) R = −H)].
[10] O. Cervinka, in 'Enamines,' ed. A. G. Cook, Marcel Dekker, New York, 1969, pp. 265—268 and references therein.