An Improved 1-Benzylisoquinoline Synthesis using Reissert Compounds as Intermediates

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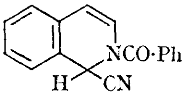
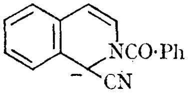
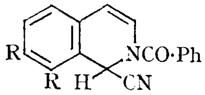
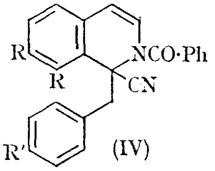
1-SUBSTITUTED isoquinolines can be prepared by use of Reissert compounds[1] (*N*-benzoyl-1,2-dihydroisoquinaldonitriles) (I) as intermediates. Action of base removes the 1-hydrogen in (I) to give the anion (II) which undergoes nucleophilic addition with alkyl halides[2] and aromatic aldehydes.[3] Anion generation is normally achieved by use of phenyl-lithium at low temperatures (−20°). However, it has recently been reported[4] that the anion (II) can be produced at room temperature by use of sodium hydride in dimethylformamide.

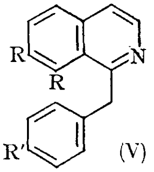
We have independently made the same observation, and have employed the reaction in the preparation of 1-benzylisoquinolines. Reaction of the Reissert compound (III; R = H), prepared by the method of Popp and Blount,[5] with benzyl chloride in the presence of sodium hydride and dimethylformamide produces the 1-benzylisoquinoline derivative (IV; $R = R' = H$). The reagents were added at 0° and the reaction mixture then stirred at room temperature for two hours, being maintained under nitrogen throughout. Alkaline hydrolysis of (IV) gives 1-benzylisoquinoline (V; $R = R' = H$) in 84% overall yield. This compares with 78% overall yield when phenyl-lithium is used as base.[2]


(I)


(II)


(III)


(IV)


(V)

The reaction is successful with other benzyl halides and with substituted isoquinolines. For example 1-anisylisoquinoline (V; $R = H$, $R' = OMe$) and 1-anisyl-7,8-dimethoxyisoquinoline (V; $R = R' = OMe$) are obtained in 72% and 32% overall yields.[6] We found use of phenyl-lithium in otherwise equivalent experiments led to 66% and 0% yields respectively. The last example gives some indication of the scope of the sodium hydride method, in view of the fact that carbanion formation and substitution has occurred with steric hindrance present in the 8-position. The same reaction failed when the phenyl anion was used as base.

Thus the use of sodium hydride in dimethylformamide at ambient temperatures in place of phenyl-lithium at −20° has the advantage that reactions are more easily carried out, give consistently better yields, and are less demanding in steric requirements. Futhermore the production of the intermediate Reissert carbanion can readily be followed by observation of hydrogen gas evolution, which is not possible in the phenyl-lithium case.

The usefulness of the method for application to the benzylisoquinoline alkaloid field is apparent and some work in this direction is currently in progress.

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[1] W. E. McEwan and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 51.
[2] V. Boekelheide and J. Weinstock, *J. Amer. Chem. Soc.*, 1952, **74**, 660.
[3] F. D. Popp and W. E. McEwan, *J. Amer. Chem. Soc.*, 1957, **79**, 3733.
[4] F. D. Popp and J. W. Wefer, *Chem. Comm.*, 1966, 207.
[5] F. D. Popp and W. Blount, *Chem. and Ind.*, 1961, 550.
[6] Satisfactory spectral and analytical data have been obtained for the products reported.