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Reductive Amination of Aromatic Aldehydes Using NADH Models

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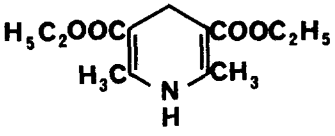
Summary: Reductive amination of aromatic aldehydes takes place when treated with equimolar amounts of aromatic amines and NADH model compounds in glacial acetic acid. Imines, the intermediates in the reaction were also reduced by NADH models in acetic acid.

Schiff's bases can be reduced by a variety of reagents[1,2] such as catalytic hydrogenation, metal-alcohol, lithium aluminium hydride, triethylamine-borane complex, and sodium borohydride. During studies[3] of 1,4-dihydropyridines as NADH models we found that compound I efficiently reduces Schiff's bases at room temperature in glacial acetic acid (Table I). Since the imines in neutral solvents in the dark are not reduced by I, obviously, protonation activates the carbon-nitrogen double bond towards reduction.



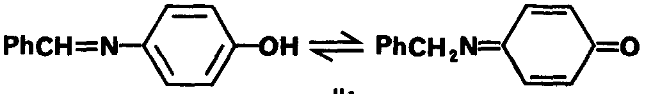
I

$ArCH{=}NAr'$

II

$ArCH_2NHAr'$

III



IIf

Since acetic acid is a very suitable medium for condensation of aldehydes and primary amines,[4] we expected reductive amination of aldehydes to take place if the aldehyde, primary amine and compound I were allowed to react in equimolar quantities in glacial acetic acid. This was indeed found to be so. The one pot reductive amination products were obtained in yields (figures in parentheses, Table I) similar to the two step procedure. Enolizable Schiff's bases such as IIf which are not reduced[2a] by complex metal hydrides are cleanly reduced by I.

Table I[5]

Imine	IIa	IIb	IIc	IId	IIe	IIf	IIg
Ar	p-$MeOC_6H_4$	C_6H_5	p-HOC_6H_4	p-$MeOC_6H_4$	C_6H_5	C_6H_5	C_6H_5
Ar'	p-$MeOC_6H_4$	2-Naphthyl	p-$MeOC_6H_4$	2-Naphthyl	p-ClC_6H_4	p-HOC_6H_4	C_6H_5
Amine III[6] (% yield)	90 (85)	89 (88)	79 (75)	78 (71)	83 (78)	95 (90)	66 (75)

Typically, the imines (II, or the corresponding aldehyde & amine, 1 mmole each) and compound I (253 mg, 1 mmole) dissolved in glacial acetic acid (10 ml) were kept at room temperature for 6 h. Addition of ice-water (100 ml), extraction with benzene, drying (anhyd. Na_2SO_4), and evaporation of the benzene solution, was followed by separation of products by column chromatography on silica gel.

Chelation of a metal ion to imine nitrogen in NADH dependent oxidoreductases is reported[7] to be responsible for activation of imines towards reduction. This it seems could equally be achieved by protonation of the imines by appropriately placed carboxylic group in the active site of the enzyme. In view of the importance of imines as intermediates in many enzyme reactions, their protonation by aliphatic carboxylic acids and reduction by NADH models is biologically significant To eliminate the necessity of chromatographic separation of products, 1,4-dihydropyridines immobilized on a polymer support are being examined which would also make regeneration and recycling of the reducing agent possible.

References and Footnotes

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5. The isolated amines (III) were characterized by comparison of m.p. and spectroscopic properties of authentic samples.
6. Imines II (1 mmole) in CH_2Cl_2 after addition of TFA (1 mmole) are reduced by I (1 mmole), but yields are somewhat lower. So is the case when N-benzyl-1,4-dihydronicotinamide is used.
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