Reduction of Imines Using NADH Models

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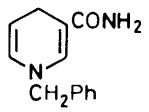
Reduction of substituted *N*-arylideneanilines (**3**) and *NN'*-bisarylidene-ethylenediamines (**10**) in glacial acetic acid takes place smoothly with 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester) (**2**) at room temperature in the dark. One-pot reductive amination of aromatic aldehydes in glacial acetic acid using (**2**) was equally efficient. Enamines (**6**)—(**8**) underwent reduction on protonation with trifluoroacetic acid in dichloromethane, but not in acetic acid. These reductions are analogous to NADH-mediated biochemical reductive aminations of carbonyl compounds. Imines (**3**) are also reduced to the corresponding amines (**4**) when irradiated with Pyrex-filtered light in the presence of (**2**) in benzene under nitrogen. This photoreduction also proceeds in the solid state and a two-phase system was successfully tested for recycling an NADH model for photoreduction of (**3**) using sunlight.

Reduction of the carbon–nitrogen double bond is an important biochemical process[1] involved in assimilation and detoxification of ammonia by condensation with α-keto acids to be followed by NAD(P)H-mediated reduction, giving rise to α-amino acids. Similar imine reduction by NAD(P)H is also crucial in dihydrofolate-mediated processes and in alkaloid biosynthesis. We report here some results of our investigations on the non-enzymatic reduction of imines using NADH model compounds.[2]

Results and Discussion

Imines as such in the dark are not reduced by the 1,4-dihydropyridine moiety in neutral medium but have to be made susceptible to reduction either by conversion into iminium compounds by alkylation or by co-ordination to metal ions. However, except for a few instances in alkaloid biosynthesis, enzymatic imine reductions involve activation of the imine by a weakly acidic group such as a carboxylic acid or a protonated imidazole present at the catalytic site. We planned to investigate the use of carboxylic acids as imine activators for reduction with 1,4-dihydropyridine compounds as NADH models. However, dihydropyridine compounds are known to be unstable in acids due to protonation of the enamine moiety to be followed by ring opening and disproportionation.[3] We found that *N*-benzyl-1,4-dihydronicotinamide (**1**) underwent very rapid decomposition in glacial acetic acid, whereas 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethylpyridine (Hantzsch ester) (**2**) was reasonably stable for brief periods at room temperature. The latter was therefore selected as the NADH model compound to be used in glacial acetic acid and *N*-arylideneanilines (**3**) as the substrate imines in view of their ease of preparation and stability in acetic acid. When equimolar amounts (1 mmol each) of the imines (**3**) and (**2**) were mixed in glacial acetic acid very good yields (Table) of the corresponding *N*-benzylanilines (**4**) were isolated along with the pyridine compound (**5**). *p*-(Benzylideneamino)phenol (**3f**), which is not reduced[4] by sodium borohydride due to tautomerism to the quinoid form, was reduced cleanly by the NADH model in glacial acetic acid. Glacial acetic acid is also known to be a good medium for the condensation of aromatic aldehydes and amines to form Schiff's bases.[5] One-pot condensation and reduction was successfully carried out by taking equimolar amounts of diester (**2**), an aromatic aldehyde, and an amine in glacial acetic acid whereby the corresponding amines (**4**) were isolated in equally good yields. This is analogous to the enzymatic process, *e.g.* in glutamate dehydrogenase, where imine formation and reduction by NADPH takes place assisted by the presence of an acidic group at the same catalytic site. *NN*-Disubstituted iminium salts have previously been reduced but not the protonated imines due in the first place to the latter's tendency to undergo easy cleavage and secondly because of their pK_a (*ca.* 2.0) which is low enough to protonate the commonly used NADH model (**1**) resulting in decomposition of the latter. We found that diester (**2**) is less susceptible to such decomposition over short periods of time. Thus, when a slight excess of trifluoroacetic acid was added to an imine (1 mmol) in dry dichloromethane followed by (**2**) (1 mmol), the amines (**4**) were isolated again in fairly good yields indicating that decomposition (if any) of (**2**) was much slower than the reduction of the protonated imine formed *in situ*. This encouraged us to attempt the *in situ* formation and reduction of *NN*-disubstituted iminium salts as well. Enamines (**6**)—(**8**) (1 mmol), prepared from cyclohexanone and secondary amines, when protonated in dichloromethane with trifluoroacetic acid and reduced with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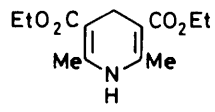
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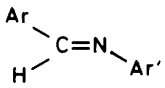
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ArCH$_2$NHAr'
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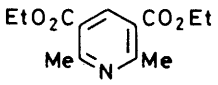
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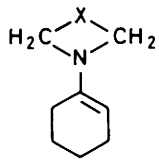
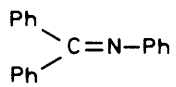

(6) X = –[CH$_2$]$_2$ –
(7) X = –[CH$_2$]$_3$ –
(8) X = –CH$_2$OCH$_2$ –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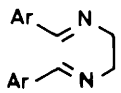
(10)

Table. Reduction of imines (**3**), (**9**), and (**10**) and enamines (**6**)—(**8**) with NADH model (**2**)

Substrate			Method[a]	Product yield (%)	M.p. (°C)[b]
Imines	Ar	Ar′			
(**3a**)	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	A	90	95
			B	85	(94—95)[c]
			C	50	
			D	92	
			F	80	
(**3b**)	Ph	2-Naphthyl	A	89	67—68
			B	88	(68)[d]
			D	77	
			F	65	
(**3c**)	*p*-HOC_6H_4	*o*-$MeOC_6H_4$	A	79	124—125
			B	75	(125)[e]
(**3d**)	*p*-$MeOC_6H_4$	2-Naphthyl	A	78	103—104
			B	71	(104.5)[d]
			D	85	
			F	75	
(**3e**)	Ph	*p*-ClC_6H_4	A	83	48—49
			B	78	(48.5—49)[f]
			C	46	138—139[g]
					(138)[f]
(**3f**)	Ph	*p*-HOC_6H_4	A	95	89
			B	90	(88—89)[h]
					170[i]
					(169—169.5)[h]
(**3g**)	Ph	Ph	A	66	108[g]
			B	75	(107—107.5)[j]
			C	90	
			D	60	
			E	55	
			F	70	
(**3h**)	*p*-MeC_6H_4	Ph	D	90	46—47
					(47)[k]
					190—191[l]
					(191)[k]
(**3i**)	*p*-HOC_6H_4	Ph	D	60	
Ketimine					
(**9**)	Ph	P	C	60	56—57
					(57)[m]
					201—202[l]
					(201—203)[m]
Bisarylidene-ethylenediamines					
(**10a**)	Ph	—	A	45	138—39[i]
					(139)[n]
(**10b**)	*p*-ClC_6H_4	—	A	50	138—140[i]
					(139—140)[h]
Enamines					
(**6**)			C	55	166—168[p]
					(167—169)[q]
(**7**)			C	58	131—132[p]
					(133)[r]
(**8**)			C	50	178[p]
					(176—177)[q]

[a] See Experimental section. [b] Known compounds, literature values in parentheses. [c] M. Julia and J. Igolen, *Bull. Soc. Chim. Fr.*, 1962, 1056. [d] L. Zeckmeister and J. Truka, *Ber.*, 1930, **63**, 2883. [e] C. A. Bischoff and E. Frohlick, *Ber.*, 1906, **39**, 3964. [f] D. H. Peacock, *J. Chem. Soc.*, 1924, **125**, 1979. [g] Of benzamide derivative. [h] J. H. Billman and J. W. McDowell, *J. Org. Chem.*, 1961, **26**, 1437. [i] Of acetamide derivative. [j] Ref. 4(*b*). [k] H. D. Law, *J. Chem. Soc.*, 1912, **101**, 154; [l] Of hydrochloride. [m] Ref. 4(*a*). [n] J. Van Alphen, *Recl. Trav. Chim. Pays-Pas*, 1935, **54**, 93. [p] Of picrate derivative. [q] R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897. [r] L. I. Zakharkin and L. A. Savina, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1964, 1695.

diester (**2**) gave the corresponding *N*-cyclohexylamines. Benzophenone anil (**9**) was similarly reduced when protonated with camphorsulphonic acid and refluxed with diester (**2**) in benzene. Bisarylidene-ethylenediamines (**10**) were reduced to the corresponding diamines with compound (**2**) in glacial acetic acid.

An alternative strategy envisaged for imine reduction was the activation of the NADH model[6] instead of the imine. It was felt that if the model were selectively irradiated it might transfer electrons to the imine in the ground state to be followed by proton transfer analogous to a similar process reported recently[7] in the case of *N*-methylacridan * and benzophenone. 1,4-Dihydropyridines are, however, known to undergo dimerization and disproportionation[3] upon irradiation. Fortunately, it

* Acridan = 9,10-dihydroacridine.

had been mentioned in the literature that the diester (**2**), due perhaps to steric hindrance, was unaffected by irradiation. We exploited this photostability by irradiating an equimolar mixture of (**2**) and the imines (**3**) in benzene under nitrogen. The amines (**4**) were isolated in good yields along with the pyridine derivative (**5**). The *N*-methyl derivative of compound (**2**) was equally effective in similar photoreduction of the *N*-benzylideneaniline (**3g**). A recycling experiment was also successful in which the *N*-methylated derivative of diester (**2**) (0.05 mmol) when added to a two-phase system consisting of *N*-benzylideneaniline (**3g**) (1 mmol) in benzene and sodium dithionite and sodium carbonate in water and stirred in bright sunlight gave *N*-benzylaniline in 70% yield. The use of amide (**1**) failed to give any product in a similar experiment. Solid-state photoreduction also took place when a layer of a mixture of compounds (**2**) and (**3g**), deposited by evaporation of an equimolar dichloromethane solution, was irradiated by exposure to a mercury lamp. The product liquefied as the reaction progressed and compound (**5**) and *N*-benzylaniline were isolated as before.

The results of this investigation provide a non-enzymatic analogy to the corresponding biochemical processes such as those mediated by glutamate dehydrogenase and other enzymes which reduce imines. The importance of activation of the imine by interaction with an acidic residue at the active site of the enzyme is thus emphasised.

Experimental

Irradiations were performed on reaction solutions in an immersion well-type Baird and Tatlock quartz photochemical reactor with a Pyrex filter using a Hanovia 125-W medium-pressure mercury vapour lamp. A Phillips 250-W medium-pressure mercury lamp was employed for solid-state photoreduction. Column chromatography was carried out using silica gel (60—200 mesh) and benzene or benzene–ethyl acetate mixture (90:10) as eluant. T.l.c. was performed with silica gel (Merck GF_{254}) in benzene–ethyl acetate (90:10) as developer. Glacial acetic acid of analytical grade (B.D.H.) was used as supplied. Dichloromethane was used after being distilled over a small quantity of phosphorus pentaoxide. Trifluoroacetic acid was obtained from Fluka and used as such. Reagent grade benzene (B.D.H.) was used after distillation and drying over sodium wire. Sodium dithionite was used either from freshly opened bottles or that preserved in a desiccator. Imines derived from aromatic amines and aldehydes were prepared by condensation in methanol whereas those derived from ethylenediamine were prepared according to the literature procedure.[8] Enamines were prepared by refluxing together the secondary amine and the ketone in benzene and azeotropic distillation of the water formed. Benzophenone anil (**9**) was similarly prepared using aniline hydrochloride as catalyst.

General Procedure for Reduction of Substrates.—(a) *In glacial acetic acid* (*Method A*). The imine (**3**) *or* (**10**) (1 mmol) and the NADH model compound (**2**) (1 mmol) were dissolved in the minimum quantity of glacial acetic acid (20 ml) at room temperature. The pale fluorescent yellow solution was left in the dark at room temperature overnight. The solution, which was colourless, indicating completion of reaction, was neutralised with aqueous sodium hydrogen carbonate and the aqueous mixture was extracted with benzene. The extract was dried (anhyd. Na_2SO_4) and evaporated to give a mixture of the amines (**4**) and (**5**) which were separated by chromatography on silica gel. The products were characterised by comparison (t.l.c., n.m.r., i.r.) with authentic samples, prepared by sodium borohydride reduction of the imines, or by preparation of the *N*-benzoyl derivative.

(b) *One-pot reductive amination of aldehydes* (*Method B*). The primary aromatic amine (1 mmol), the aromatic aldehyde (1 mmol), and the NADH model compound (**2**) (1 mmol) were dissolved in glacial acetic acid (20 ml) at room temperature. After the reaction had progressed overnight, the reaction mixture was neutralised and the products characterised as in (a).

(c) *Iminium salt reduction in dichloromethane* (*Method C*). An imine (**3**) (1 mmol) or an enamine (**6**)—(**8**) (1 mmol) was dissolved in dry dichloromethane (10 ml) and trifluoroacetic acid (0.2 ml) followed by the NADH model (**2**) (1 mmol) were added. The pale fluorescent yellow solution was left overnight in the dark. The completion of the reaction was checked by t.l.c. and the solvent was evaporated off. The residue was suspended in aqueous sodium carbonate and extracted with ether. The extract when dried (anhyd. Na_2SO_4) and evaporated gave, on chromatography, the products which were characterised as in (a). Benzophenone anil (**9**) was similarly reduced except that camphor-10-sulphonic acid instead of trifluoroacetic acid was used.

(d) *Photoreduction of imines in solution* (*Method D*). An imine (**3**) (1 mmol) and the NADH model (**2**) (1 mmol) were dissolved in benzene (180 ml) in a photochemical reactor and the solution was flushed with oxygen-free nitrogen. The mercury vapour lamp was turned on and the reaction was followed either by t.l.c. or by the disappearance of the absorption band at $\lambda_{max.}$ 372 nm. At the end of the reaction (2 h) the solvent was evaporated off, the residue was chromatographed on silica gel, and the products were characterised as in (a).

(e) *Solid-state photoreduction* (*Method E*). *N*-Benzylideneaniline (**3g**) (181 mg, 1 mmol) and compound (**2**) (253 mg, 1 mmol) were dissolved in dichloromethane (100 ml) in the dark. The solution was evaporated using a stream of oxygen-free nitrogen in the dark while the solution was gently swirled so that an amorphous layer of solid reactants deposited on the walls of the container. The latter was kept at a distance of 20 cm from a 250-W mercury vapour lamp while the container was turned occasionally to expose fresh surface to light. After nearly 10 h almost all the solid had turned into a colourless oil which was chromatographed and characterised as above to give *N*-benzylaniline (**4g**) (55%) and diester (**5**) (95%).

(f) *By recyclisation of NADH model* (*Method F*). To a solution of an imine (**3**) (1 mmol) in benzene (200 ml) was added a solution of sodium dithionite (1.5 g) and sodium carbonate (4.5 g) in water (200 ml). To this mixture was added the *N*-methyl derivative of diester (**2**) (15 mg, 0.05 mmol) and the whole mixture was stirred magnetically in bright sunlight. The progress of the reaction was monitored by t.l.c. of the benzene layer until the complete disappearance of the imine. The benzene layer was separated, washed with water, dried (anhyd. Na_2SO_4), and evaporated. The crude residue on elution through a column yielded the corresponding amine (**4**).

Acknowledgements

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