Asymmetric Reduction of Schiff's Bases with Lithium Aluminium Hydride–Monosaccharide Complexes to Give Optically Active Secondary Amines

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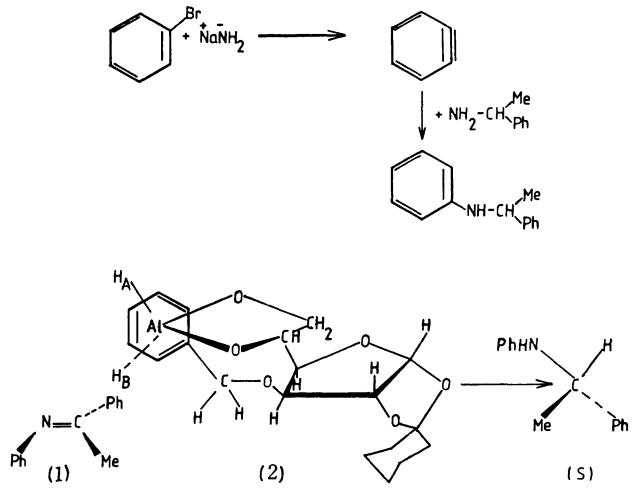
The asymmetric reduction of selected Schiff's bases (ketimines) with the lithium aluminium hydride–monosaccharide complexes derived from 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose gives optically active secondary amines. The absolute configuration of *N*-(1-phenylethyl)aniline was assigned as *S* by *N*-phenylation of *S*-(−)-1-phenylethylamine and hence all the levo-rotatory secondary amines obtained by this asymmetric reduction are assigned the *S*-configuration.

The asymmetric reduction of ketoximes and their *O*-substituted ether derivatives with the lithium aluminium hydride–monosaccharide complexes has been reported by us to give optically active primary amines.[1] We have now extended these investigations to the reduction of structurally related Schiff's bases (ketimines) to give optically active secondary amines. Prior to this investigation, an asymmetric reduction of ketimines was briefly reported by Cervinka and Suchan[2] who obtained "partially optically active primary amine". The primary amines so obtained were of low optical yields and have known configurations. More recently, Solladie and his coworker[3] described the introduction of a new chiral site on an *N*-chirally substituted imine by stereoselective reduction followed by subsequent hydrogenolysis of the chiral substituent on the nitrogen to give an optically active primary amine.



(1) (2) (S)

The reduction of ketimines with lithium aluminium hydride–3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex (**2**) follows the same pattern as that of the oxime and oxime ethers.[1] A similar mechanism is therefore postulated for the reduction of ketimines and this is shown in **1** and **2**. A preferential hydride transfer of the less shielded H_B to the carbon of the imino group with the phenyl pointing away from the shielding 3-*O*-benzyl group of the monosaccharide derivative is predicted to give optically active secondary amines of the *S*-configuration. The *N*-phenyl group is as remote from the carbohydrate moiety as the tetrahydropyranyloxy group is in the reduction of ketone oxime ethers and, therefore, not likely to play any part in the stereoselective process. The stereoselectivity of the reduction process would thus be determined by the steric and electronic interactions between the *C*-phenyl and alkyl substituents on the ketimines and the 3-*O*-benzyl group of the carbohydrate residue.

Four examples of a homologous series of ketimines were reduced with the lithium aluminium hydride complex **2** (Table 1) and gave optically active secondary amines, all levo-rotatory, which were characterised by IR, NMR, and elemental analysis (Table 2).

The absolute configuration of *N*-(1-phenylethyl)aniline was previously reported by Wittig and Thiele.[4] A confirmation of this configuration was obtained for *N*-(1-phenylethyl)aniline by phenylation *via* the benzyne of (+)- and (−)-1-phenylethylamine and comparison of the products with that obtained from the reduction of the amine. Benzyne, generated by the action of sodamide on bromobenzene in liquid ammonia,[5] reacted with *S*-(−)-1-phenylethylamine[6,7] to give (−)-*N*-(1-phenylethyl)aniline which therefore has the *S*-configuration. This method should give minimum racemisation of the optically active amine and the optical purity of the *N*-(1-phenylethyl)aniline is estimated to be >95%. This value is much greater than the 40% ee reported by Kagan *et al.*[8] The maximum specific rotation obtained was −6.2° which was used to calculate the stereoselectivity of the asymmetric reduction and gave a maximum of excess enantiomer of 23.6% (Table 3).

The three other amines for which the configuration has not been determined previously are now assigned the *S*-configuration on the basis that in our laboratory, the asymmetric reduction with this reagent of 40 compounds comprising ketones, oximes, oxime ethers, and now ketimines has without exception given products with the *S*-configuration.[1,9]

Several methods for the synthesis of ketimines have been reported in the literature.[10] Recently, the condensation of a ketone with a primary aromatic amine in the presence of hydrogen cyanide was briefly reported to give α-amino nitriles in good yields, and these were coverted into the ketimines with methanolic potassium

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Table 1. Reduction of ketimines with the aluminium hydride complex of 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose

Ketimine PhRC=NPh	*N*-(1-Phenylethylidene)-aniline (R=CH_3)			*N*-(1-Phenylpropylidene)-aniline (R=CH_2CH_3)			*N*-(1-Phenylbutylidene)-aniline (R=$CH_3CH_2CH_2$)			*N*-(1-Phenyl-2-methylpropylidene)aniline (R=$(CH_3)_2CH$)		
Secondary amine	*N*-(1-Phenylethyl)aniline[a]			*N*-(1-Phenylpropyl)-aniline[b]			*N*-(1-Phenylbutyl)aniline[c]*			*N*-(1-Phenyl-2-methylpropyl)aniline[d]*		
$LiAlH_4$ (mol)	α_D^{20} / °	% e.e.†		α_D^{20} / °	% e.e.†		α_D^{20} / °	% e.e.		α_D^{20} / °	% e,e.	
0.012	−0.71	11.5	*S*	−1.08	—	*S*††	−1.40	—	*S*††	−1.26	—	*S*††
0.018	−0.98	15.8	*S*	−1.13	—	*S*	−1.54	—	*S*	−1.45	—	*S*
0.025	−1.46	23.6	*S*	−1.54	—	*S*	−1.65	—	*S*	−1.53	—	*S*
0.032	−0.94	15.2	*S*	−1.30	—	*S*	−1.66	—	*S*	−1.54	—	*S*
0.039	−0.66	10.7	*S*	−0.90	—	*S*	−1.30	—	*S*	−1.44	—	*S*
0.045	−0.58	9.4	*S*	−0.76	—	*S*	−1.08	—	*S*	−1.38	—	*S*

a) Bp 142 °C/1.5 mmHg(1 mm Hg≈133.322 Pa); b) Bp 150 °C/1.5 mmHg; c) Mp 51—52 °C; d) Mp 54—55 °C.
*: Rotations determined for chloroform solutions (*ca.* 50%). †: Maximum specific rotation obtained from this work $[\alpha]_D^{20}$ −6.20°; % excess enantiomers. ††: Configurational assignment on the basis of present work.

hydroxide at room temperature.[11]

$$R'COR + PhNH_2 + KCN \xrightarrow{HOAC} RR'C(CN)NHPh \xrightarrow{KOH\text{-}MeOH} RR'C{=}NPh$$

In our laboratory, the elimination of hydrogen cyanide from the α-amino nitrile did not proceed in reasonable yield at room temperature, but excellent yields were obtained when the reaction was carried out under reflux for 1 h. The four examples of homologous series of ketimines used for these asymmetric reductions were synthesized by this method, and their structures confirmed by IR, UV, and NMR spectroscopy and their elemental analyses.

Experimental

Thin layer chromatography of carbohydrate derivates was performed on silica gel with benzene–methanol (98:2) as solvent system and a 1,3-naphthalenediol–phosphoric acid spray for detection. The ester used in the reductions was repeatedly dried over sodium. The purity of the amines was established by GLC on a 5 ft glass column of Carbowax 20 M on Chromosorb W (for the liquid amines), and by several recrystallizations with constant melting points were obtained (in the case of the solid amines). Optical rotations (0.01°) were determined for neat samples unless otherwise stated, with a Stanley photoelectric polarimeter and/or with a Perkin-Elmer 141 polarimeter at 20 °C. NMR spectra were obtained for solutions in deuteriochloroform with Varian A60 and T60 spectrometers, tetramethylsilane being used as internal reference.

Preparation of α-Amino Nitrile. The ketone (0.66 mol) and aniline (6.12 g, 0.06 mol) were dissolved in glacial acetic acid (25 ml). The mixture was gently stirred at 0 °C while portions of solid potassium cyanide (4.3 g, 0.66 mol) were cautiously added. Stirring was continued until a solid crystallized (*ca.* 1 h). The mixture was then cooled and filtered; the solid residue was washed with water (4×100 ml) and light petroleum (bp 40—60 °C; 4×50 ml) and then crystallized from methanol, yields 80—90% ν_{max} 2230 (CN) and 3400 cm^{-1} (NH).

Preparation of Ketimines. The α-amino nitrile (0.03 mol) was dissolved in hot methanol (40 ml). To this a solution of potassium hydroxide (6.7 g, 0.12 mol) in methanol (50 ml) was carefully added and the reaction mixture heated under reflux for 1 h. Water (100 ml) was added to the cooled mixture and the organic material removed by extraction with light petroleum (bp 40—60 °C; 4×50 ml). The combined light petroleum extracts were washed with water (2×100 ml), dried ($MgSO_4$) and the solvent evaporated to give a light yellow oil which was refrigerated. The crude solid material was recrystallized from light petroleum (bp 40—60 °C) to give the pure ketimine; ν_{max} 1640—1650 cm^{-1} (C=N).

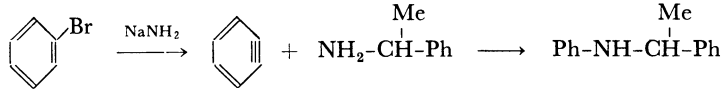
Reduction of Ketimines with the Lithium Aluminium Hydride–3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose Complex. A solution of the glucofuranose (8.8 g, 0.025 mol) in dty ether (50 ml) was added to a measured volume of a standardized ethereal solution of lithium aluminium hydride (*ca.* 18—20 g l^{-1}). The mixture was heated under reflux for 90 min, after which a solution of the ketimine (0.025 mol) in dry ether (20 ml) was added. Heating under reflux was continued for 2.5 h, after which the mixture was cooled, the complex decomposed with water (15 ml) and the precipitated hydroxide filtered off and washed with ether (2×30 ml). The combined filtrate and washings were extracted with dilute hydrochloric acid (3×20 ml) to separate all basic components. The aqueous acid layer was strongly basified (6 M† NaOH) and extracted with ether (3×50 ml) and the extract washed with water (2×30 ml) and dried ($MgSO_4$). Evaporation gave an oily porduct. The optically active secondary amine was isolated by fractional distillation under reduced pressure and characterized by IR, NMR spectroscopy, and elemental analysis; its purity was checked by GLC or by recrystallization in the case of a solid product (Table 2).

Determination of the Absolute Configuration of N-(1-phenylethyl)-aniline. Metallic sodium (0.58 g, 0.025 mol) and an excess of liquid ammonia (20 ml) were stirred for 1 h, after which bromobenzene (4 g, 0.025 mol) was added. The resultant dark violet product was further stirred for 1 h, after which 1-phenylethylamine (3.0 g, 0.025 mol) was added dropwise with stirring. Stirring was continued for another 3 h, the reaction mixture was neutralized with dilute hydrochloric acid (3×10 ml) and the aqueous layer strongly basified (6 M NaOH). Work-up gave an oily product which was distilled under reduced pressure and then characterized by IR and NMR spectroscopy; the optical rotation

† 1 M=1 mol dm^{-3}.

Table 2. Physical and analytical data ketimines and *N*-(1-phenylalkyl)anilines

	C_6H_5-C(R)=N-C_6H_5 Chemical shifts (in τ values)		C_6H_5-CH(R)-NH-C_6H_5 Chemical shifts (in τ values)				Bp θ_b / Mp θ_m /°C at 1.5 mmHg	Yield/%	Analyses (%) Found			Calcd		
R	$2\times C_6H_5$	R	$2\times C_6H_5$	H	R	NH			C	H	N	C	H	N
Me	2.0—3.5 (10H, m)	7.38(3H, s, CH_3)	2.63—3.70 (10H, m)	5.60 (1H, dd-CH)	8.60 (3H, d, CH_3)	6.20	142	76	85.25	7.45	7.15	85.30	7.60	7.10
Et	2.0—3.4 (10H, m)	9.0(3H, t, CH_3) 7.45(2H, dd, CH_2)	2.70—3.70 (10H, m)	5.70 (1H, t, -CH)	8.40(2H, dp-CH_2) 9.20(3H, t, CH_3)	6.30	150	80	85.21	7.91	6.45	85.31	8.09	6.60
Pr	2.4—3.6 (10H, m)	9.08(3H, t, CH_3) 8.55(2H, m, CH_2) 8.00(2H, t, CH_2)	2.70—3.70 (10H, m)	5.70 (1H, t, -CH)	8.40(2H, M, CH_2) 8.82(2H, m, CH_2) 9.25(3H, t, CH_3)	6.35	51—52 mp	75	85.12	8.71	6.38	85.35	8.44	6.22
Pr^i	2.6—3.6 (10H, m)	8.80(3H, d, CH_3) 8.60(3H, d, CH_3) 7.05(1H, dd, CH)	2.75—2.60 (10H, m)	5.90 (1H, d, CH)	8.65(1H, m, CH) 9.30(3H, d, CH_3) 9.35(3H, d, CH_3)		54—55 mp	78	85.07	8.75	6.34	85.34	8.44	6.22

Table 3. 

Liq NH_3 (ml)	Na (g)	C_6H_5Br (g)	1-Phenylethylamine : g rotation	*N*-(1-Phenylethyl)aniline	Yield g	Yield %	$[\alpha]_D^{20}$ °	Solvent	Concn %
20	0.58	4.0	3.0 (±)	(±) 140 °C/1.3 mmHg	3.2	64	—	—	—
20	0.58	4.0	3.0 (−) $[\alpha]_D^{20}$ −38.5°*	(−) 142 °C/1.5 mmHg	3.7	74	−6.2	$CHCl_3$	50
20	0.58	4.0	3.0 (+) $[\alpha]_D^{20}$ +38.5*	(+) 142° C/1.5 mmHg	3.4	68	+6.0	$CHCl_3$	50

*: Supplied by E. Merck, Darmstadt.

was determined.

References

1) S. R. Landor, O. O. Sonola, and A. R. Tatchell, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1902.
2) O. Cervinka, V. Suchan, O. Kotynek, and V. Dudek, *Collect. Czech. Chem. Commun.*, **30**, 2484 (1965).
3) G. Solladie and G. Demailly, *Tetrahedron Lett.*, **1975**, 2471.
4) G. Wittig and U. Thiele, *Justus Liebigs Ann. Chem.*, **726**, 1 (1969).
5) I. Tabushi, K. Okazaki, and R. Oda, *Tetrahedron Lett.*, **1967**, 3827.
6) A. W. Ingeroll, *Org. Synth*, Coll. Voll. II, 503 (1943).
7) W. Leither, *Ber.*, **64**, 2827 (1931).
8) H. B. Kagan, N. Langlois, and T. P. Dang, *J. Organomet. Chem.*, **90**, 353 (1975).
9) S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc., C*, **1966**, 1822; **1966**, 2280; **1967**, 197.
10) R. W. Layer, *Chem. Rev.* **63**, 498 (1963).
11) J. S. Walia, L. Heindl, H. Lader, and P. S. Walia, *Chem. Ind.*, **1968**, 155.
12) H. Felkin, *Bull. Soc. Chim. Fr.*, **1951**, 347.