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Reductive Amination of 1,4- and 1,5-Dicarbonyl Compounds with (S)-Valine Methyl Ester. Synthesis of (S)-2-Phenylpyrrolidine and (S)-2-Phenylpiperidine.

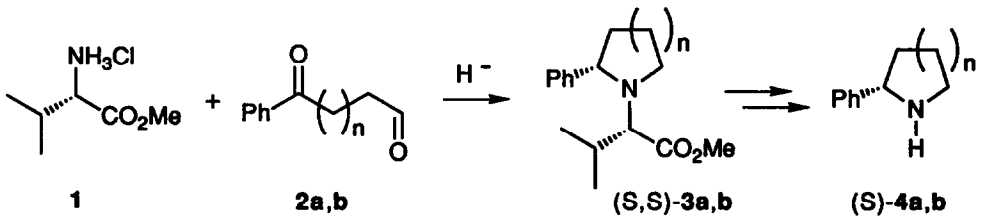
Francesco Manescalchi, Anna R. Nardi, and Diego Savoia*

Dipartimento di Chimica "G.Ciamician", Università di Bologna, via Selmi 2, 40126 Bologna, Italy

Abstract: The reductive amination of 4-phenyl-4-oxobutanal and 5-phenyl-5-oxopentanal with (S)-valine methyl ester and sodium cyanoborohydride afforded the N-substituted (S)-2-phenylpyrrolidine (88% d.e.) and (S)-2-phenylpiperidine (96% d.e.), from which the levorotatory N-H cyclic amines were obtained. On the other hand, the analogous reductive amination of simple ketones, 2,5 hexanedione, and 2,6-heptanedione was poorly selective.

The reductive amination of carbonyl compounds,[1] including the Leuckart reaction,[2] is a convenient method for the preparation of amines. However, the application to the synthesis of optically active amines from prochiral ketones and homochiral primary amines is lacking heretofore.[3] In fact, the electrochemical reduction of the mixture of 2-hexanone and excess (R)-2-amino-1-butanol in methanol-water solution gave a very low level of asymmetric induction.[4] It has been obtained up to 74% d.e. in the reductive amination of 4-phenyl-2-oxobutanoic acid with alanine esters and dipeptides by using catecholborane as reducing agent, but poor diastereoselectivity was obtained with sodium cyanoborohydride and by catalytic hydrogenation.[5]

We have undertaken a systematic study on the reductive amination of carbonyl and dicarbonyl compounds with (S)-valine methyl ester hydrochloride (**1**) and several reducing agents, principally borohydrides. We observed that high level of asymmetric induction was achieved in the reductive aminocyclization reactions of the ketoaldehydes **2a,b**,[6] affording the cyclic amines **3a,b**, which are precursors of 2-phenylpyrrolidine and -piperidine (**4a,b**) (Scheme 1).

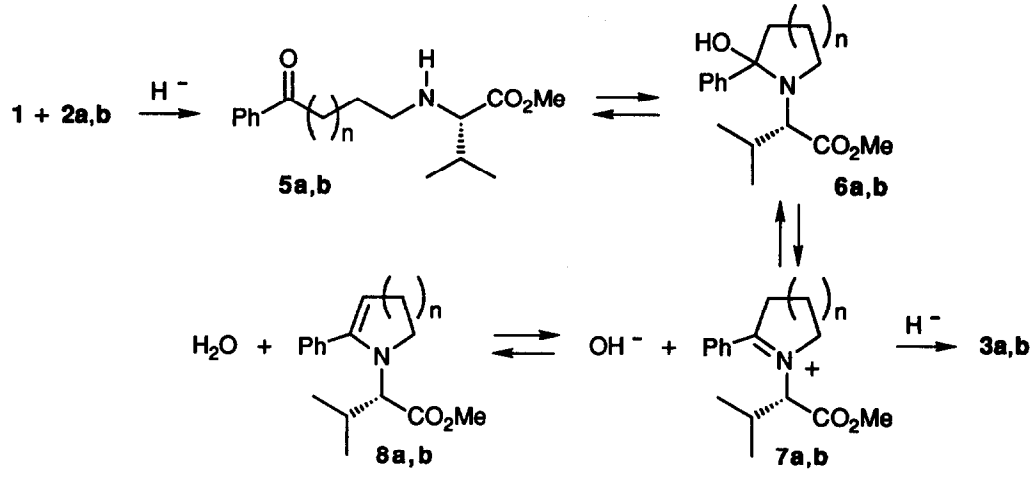


1 **2a,b** (S,S)-**3a,b** (S)-**4a,b**

Scheme 1. **a** : n = 1 ; **b** : n = 2.

The rate and efficiency of the reaction were found dependent on the size of the ring formed. It was established that the formation of the corresponding pyrrole from the γ-ketoaldehyde **2a** was not a serious problem, and that the cyclic enamines **8a,b** were more important byproducts, especially in the construction of

the piperidine ring. In fact the reaction pathway (Scheme 2) involves two subsequent reductive amination steps, firstly on the aldehyde (**2a,b** to **5a,b**) and then, intramolecularly, on the ketone (**5a,b** to **3a,b**). We assume that the aminoketones **5a,b** and the cyclic enamines **8a,b** should reach the equilibrium[9] through the cyclic aminoketals **6a,b** and the iminium ions **7a,b**, from which **3a,b** are derived by hydride addition.



Scheme 2. **a** : n = 1 ; **b** : n = 2.

The experimental results are reported in Table 1. The pyrrolidine **3a** was formed more rapidly and cleanly than the piperidine **3b** by working with sodium cyanoborohydride in methanol at 0-25° (compare entries 1 and 3). Following the reaction course by GC-MS analysis, we ascertained that **2a** disappeared quickly even at -20°, being converted to the cyclic enamine **8a** and the pyrrolidine **3a**, but we never detected the aminoketone **5a**. They were necessary approximately 12h at room temperature to achieve the almost complete conversion of **8a** to **3a**, which was obtained with good diastereoselectivity (88-90% d.e.).

On the other hand, the preparation of the piperidine **3b** from **2b** was less efficient in the same experimental conditions, since the cyclic enamine **8b** persisted in the reaction mixture in discrete amount after 24h. Furthermore, the aminoketone **5b** was present in considerable amounts when the reaction was performed in methanol at -30° (entry 4), and in tetrahydrofuran (entry 6), where the reaction was exceedingly low even at room temperature. Dichloromethane was also a suitable solvent (entry 5), as only traces of **8b** were observed after 24h, but the diastereoisomeric excess of **3b** was slightly lower with respect to that obtained in methanol.

Keeping lower the initial temperature (-15 for **2a**, -30° for **2b**) in methanol the diastereoselectivity was not improved significatively (entries 2 and 4). Furthermore, by employing sodium triacetoxyborohydride as reducing agent either in dichloromethane and tetrahydrofuran, the piperidine **3b** was cleanly produced, but with modest diastereoselectivity (entries 7, 8).

The configuration of the prevalent diastereoisomers of **3a,b** was demonstrated by conversion to the known optically active 2-phenylpyrrolidine (**4a**)[10] and 2-phenylpiperidine (**4b**)[11] through the removal of the nitrogen substituent. This was accomplished by a sequence of steps that involves the hydrolysis of the ester group (t-BuOK, Et_2O, H_2O),[12] and the Curtius rearrangement of the acylazide derived from the carboxylic

acid, as reported for the analogous removal of the chiral auxiliary group from the Diels-Alder cycloadducts of Brassard's diene with an imine derived from valine tert-butyl ester.[13] As **4a,b**, obtained in 50-55% yield from **3a,b**, were levorotatory, they possessed the S configuration at the chiral centre.

Table 1. Reductive Amination of **2a,b** with **1** and Hydride Reagents.[a]

Entry	Compd	Solvent	Hydride	Temp. (°C)	Time (h)	Yield (%)	3 : 8 : 5 (%)[b]	D.e.(%) of 3[b]
1	**2a**	MeOH	$NaBH_3CN$	0 to 25	12	99[c]	94 : 6 : 0	88
						96[d]	99 : 1 : 0	88
2	**2a**	MeOH	$NaBH_3CN$	-15	4	75[c]	76 : 24 : 0	90
3	**2b**	MeOH	$NaBH_3CN$	0 to 25	24	88[d]	88 : 12 : 0	96
4	**2b**	MeOH	$NaBH_3CN$	-30	6	98[c]	5 : 43 : 50	-
				to 25	36	99[c], 81[d]	88 : 12 : 0	96
5	**2b**	CH_2Cl_2	$NaBH_3CN$	0 to 25	24	99[c]	98 : 2 : 0	92
6	**2b**	THF	$NaBH_3CN$	0 to 25	24	95[c]	8 : 55 : 32	-
					72	99[c]	33 : 42 : 25	94
7	**2b**	CH_2Cl_2	$NaBH(OAc)_3$	0 to 25	24	100[c]	100 : 0 : 0	58
8	**2b**	THF	$NaBH(OAc)_3$	0 to 25	24	84[d]	100 : 0 : 0	52

(a) Unless otherwise indicated, the reactions were performed in 1-20 mmol scale by adding **2** slowly (5-60 min, according to the reaction scale) to a mixture of **1** (1 equiv.), sodium cyanoborohydride (1 molar equiv.) or sodium triacetoxyborohydride (1 equiv.), powdered KOH (1 equiv.) and AcOH (0.5 equiv.) in the indicated solvent (3-60 ml) at 0° and by stirring with a magnetic bar for 4-6 h, then the temperature was allowed to reach 25°, the solvent (MeOH or THF) was evaporated, 10% aq NaOH was added, and the amines were extracted with Et_2O (CH_2Cl_2 in entries 5 and 7). (b) Ratios evaluated by GC-MS analysis. (c) Yield of the product mixture, based on unreacted **2** and determined by GC-MS analysis. (d) Yield of crude, isolated product.

The excellent diastereoselectivity observed in the reductive aminocyclization of the ketoaldehydes **2a,b**, is certainly due to the cyclic structure of the key intermediates **7a,b**. In fact, the reductive amination of 2-octanone and acetophenone with (S)-valine methyl ester and cyanoborohydride in methanol afforded the corresponding secondary amines without stereocontrol (2-8% d.e.). Furthermore, the analogous reductive amination of the homologous diketones **9a,b** afforded the cyclic amines **10a,b** with moderate *cis-trans* selectivity,[14] but with low asymmetric induction, as the *trans* isomers were obtained as mixtures of diastereoisomers, owing to the inefficient asymmetric induction in the first reductive amination step (Scheme 3). We have obtained similar results with **9a,b** and (S)-1-phenylethylamine.[16]

Work is in progress to extend the scope of the reported reductive aminocyclization reaction to alkyl- and heteroaryl- substituted ketoaldehydes, as well as to develop a more rapid and convenient procedure to remove the valine-derived nitrogen substituent from the tertiary cyclic amines.

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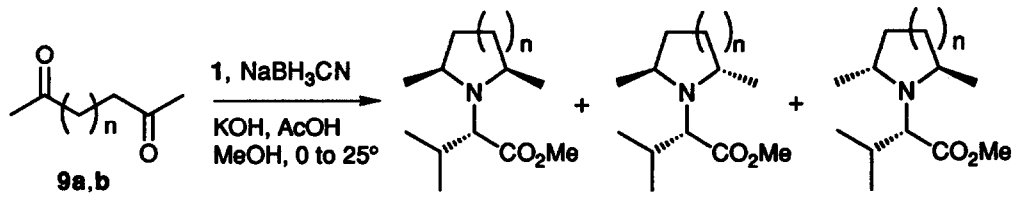

cis-(S,S,R)-**10a,b** *trans*-(S,S,S)-**10a,b** *trans*-(S,R,R)-**10a,b**

10a : 89%; *cis* : *trans* = 84 : 16 ; (S,S,S) : (S,R,R) = 50 : 50.
10b : 84%; *cis* : *trans* = 17 : 83 ; (S,S,S) : (S,R,R) = 34 : 66 , or viceversa.

Scheme 3. **a** : n = 1 ; **b** : n = 2

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