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# Asymmetric Reductions with Freely and Non-freely Rotating Amide Group NADH Models

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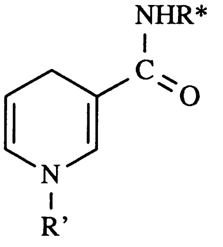
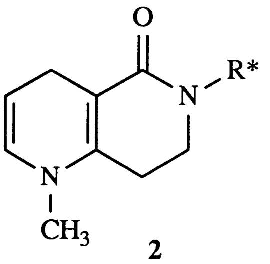
NADH models with a freely or non freely rotating chiral amide group have been synthesized and used in the reduction of methyl benzoylformate. The same major enantiomer was obtained in all cases. A blocked reagent bearing a phenylalaninol group as chiral auxiliary allows one to obtain a high e.e.

NADH models are promising reagents in reduction. The design, however, of readily accessible NADH model compounds combining high reactivity and complete enantioselectivity still remains a challenge. Some asymmetric reductions of prochiral ketones such as methyl benzoylformate have been performed with high e.e. 1) It is essential in the model system to use a metal ion ($Mg^{2+}$) in order to facilitate reaction and, moreover, to facilitate stereocontrol during the hydride transfer step.

Generally, with common chiral models, it is the polar function at C-3 which, by chelation, ensures the preferential availability of only one of the prochiral hydrogens at C-4.1a) Many points still remain unclear concerning the precise orientation of the partners in the ternary complex constructed between the reagent, $Mg^{2+}$ and the substrate.2) It is generally assumed that the oxygen of the amide carbonyl points towards the 2-position of the dihydropyridine ring (may be through a secondary interaction with the ring nitrogen (Ref.1a p. 19)) and that the carbonyl oxygen of the substrate also points towards the ring nitrogen due to the binding by $Mg^{2+}$.1a) The most widely described models have freely rotating amide part, so the hypothesis concerning the molecular arrangement is plausible. Other possibilities may be envisaged, e.g. the two carbonyls can point in opposite directions. It could be of interest to perform an asymmetric reduction with a model where the position of the amide carbonyl is blocked for example in a cyclized structure. As a consequence, such a model limits the freedom concerning the number of degrees of one of the partners in the ternary complex. Moreover this feature is interesting in connection with a theoritical study in which the geometry of the carbonyl group in nicotinamide is correlated with the reactivity of NAD(P)H coenzyme.3)



**1**

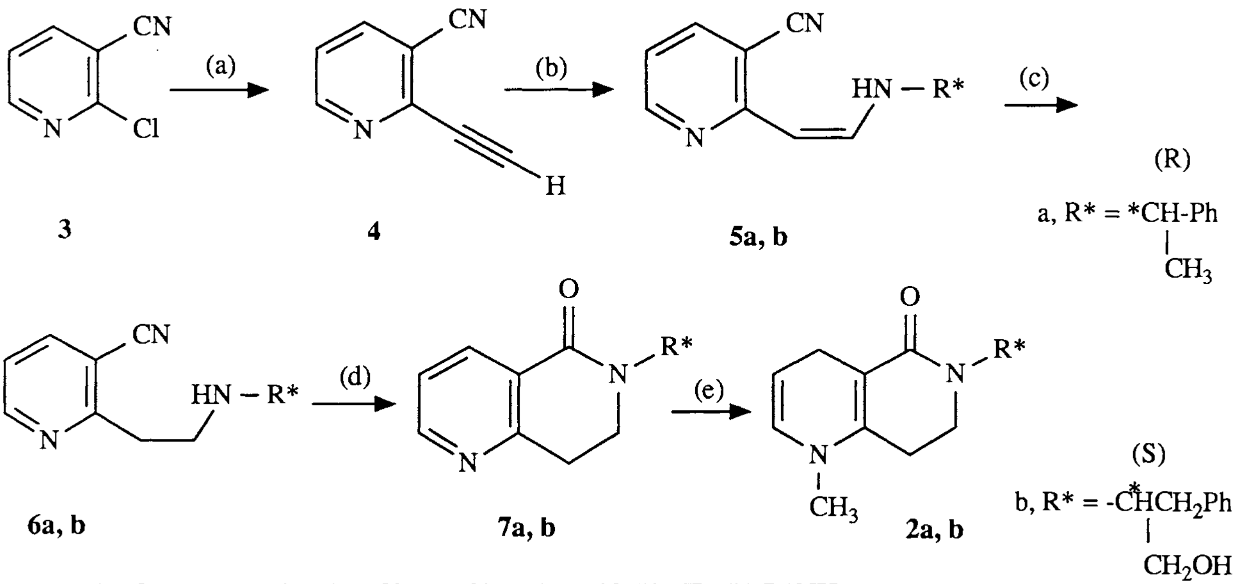


**2**

Herein we describe the synthesis of type **1** and **2** NADH models where the geometry of the carbonyl part of the amide is free or blocked in a cyclized structure. The behaviour of the two types of reagents will be compared by performing the reduction of methyl benzoylformate.

Reagent **1a** (R=(-CH($CH_3$)Ph(R)); R'=n.$C_3H_7$) has been described in the literature.[4]

Reagent **1b** (R=-CH($CH_2OH$)$CH_2$Ph(S); R'=$CH_3$) was obtained by an adaptation of a previously described method:[1d] condensation between nicotinoyl chloride and (S) phenylalaninol followed by quaternization with methyl iodide and regioselective reduction with $Na_2S_2O_4$. Reagents **2a, b** were synthesized by following the strategy outlined in Scheme 1.



(a) CuI, $NEt_3$, $Pd[PPh_3]_2Cl_2$,$Me_3Si$-≡, then KOH/THF; (b) $R^*NH_2$;
(c) $NaBH_3CN/ZnCl_2$; (d) EtOH, $H_2O$; (e) $CH_3I$, then $Na_2S_2O_4/Na_2CO_3$.

Scheme 1. Synthesis of reagents **2a, b.**

The key step of the synthesis was the cross coupling reaction of the readily available 2-chloropyridine-3 carbonitrile with trimethylsilylacetylene in the presence of a palladium catalyst.[5] The coupled product was then desilylated under mild conditions to afford the ethynyl compound which was subsequently aminated with chiral amines. After reduction of the enamine and ring closure, we obtained 6-N substituted 1,6-naphtyridin-5(6H)-ones **7a, b** with a very good overall yield. During the synthesis, no racemization occured.[6] The dihydropyridine derivatives **2a, b** were obtained by conventional methods.

With the reagents **1a, b** and **2a, b** so obtained reduction of alkyl benzoylformate gave the results summarized in Table 1.

Table 1. Reduction of alkyl benzoylformate with **1a, b** and **2a, b**

| Reagent | **1a** a)<br>(4) | **2a** | **1b** | **2b** |
|---|---|---|---|---|
| Reagent configuration | (R) | (R) | (S) | (S) |
| Chemical yield/% | 100 | 72 | 60 | 54 |
| e.e. % b) | 20 | 20 | 57 | 85 |
| Product configuration | (R) | (R) | (R) | (R) |

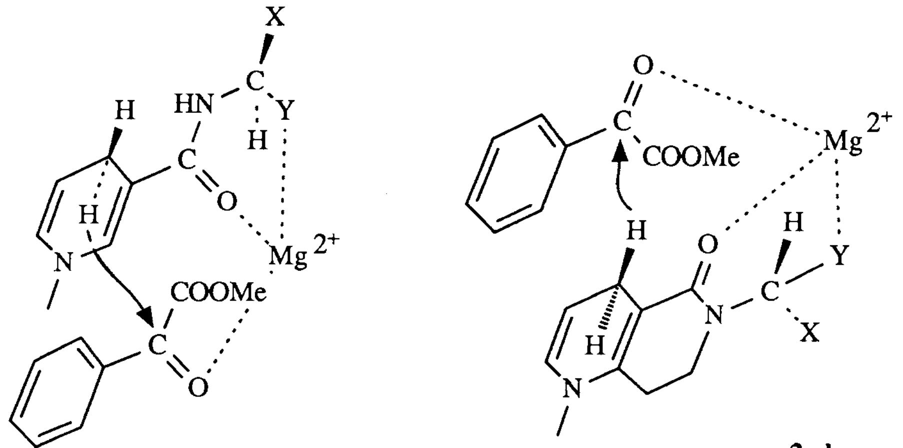
a) With **1a** ethyl benzoylformate was used, with **1b** and **2a, b** the methyl ester was used.

b) Determined by optical rotation or by HPLC analysis by using a chiral column.

Reactions were performed at room temperature for **1a** or at 60 °C for **1b, 2a, b** in $CH_3CN$ with a molar ratio, reagent/$Mg^{2+}$/substrate: 1/1/1.

As can be seen from the table the major enantiomer was the same both from reagent of type **1** or of type **2**.

Assuming that in the ternary complex the phenyl and the 1,4-dihydropyridine rings are facing each other and that the carbonyl groups of the ketone and the amide are also facing each other via complexation of the magnesium,[1a)] the transition state can be depicted as in figure 1. In all cases it appears that the predominant obtention of the (R)-methyl mandelate is best explained by the transition states where the two carbonyls are pointing in the same direction. The results with **2a, 2b** show that the carbonyl of the amide can point in the opposite direction of pyridine contrary to the idea generally admitted.[7)]



**1a,b**

**2a,b**

**1a** X = Ph

**2a** Y = $CH_3$

**1b** X = $CH_2Ph$

**2b** Y = $CH_2OH$

The complexation with Y occurs only when Y = $CH_2OH$.

Fig. 1. Structure of the ternary complex with reagents **1** or **2a,b**.

Moreover it is of interest to observ that the rigidity of the chiral reagent **2b** causes a dramatic enhancement of the e.e. compared to **1b** (57 to 85 %). This result thus demonstrates that reagent **2b** is indeed very promising in the reduction of prochiral ketones.

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6) Compounds **2, 5, 6, 7** are new. Satisfactory analysis and spectral data were obtained. Several problems had to be solved during their synthesis which will be described later.

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