

## Study of the Reduction of Enamides with an NADH Model

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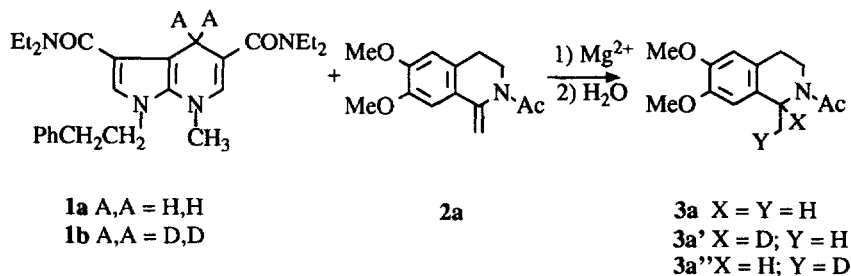
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*Key words:* enamide, NADH model, reduction, mechanism

**Abstract :** The regioselectivity of the reduction of the cyclic enamide **2a** with an NADH model compound was established using a deuterated model. The geometry of the substrate seems to play a fundamental role since cyclic derivatives **2a** and **2d** were reduced and non cyclic derivatives **2b** and **2c** were not reduced. Electronic factors were also examined.

Enamides (N-acylenamines) are successfully reduced by catalytic hydrogenation <sup>1</sup>. There is only one example to our knowledge where an enamide was reduced with an hydride donor <sup>2</sup>.

In a recent paper we reported the successful reduction of the carbon-carbon double bond of the tertiary enamide **2a** with an NADH model **1a** <sup>3</sup> leading, after proper transformations, to racemic salsolidine.



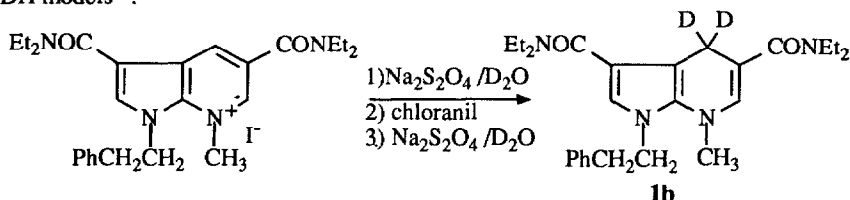
The literature precedence concerning the reduction of ethylenic compounds with NADH models is extremely sparse. In all cases the unsaturated bond was activated by the presence of a powerful withdrawing group <sup>4</sup>. In a tertiary enamide the behaviour is quite different. Hence, with the view to obtaining information about the reduction of these substrates we decided to perform two series of experiments.

### *Site of attack of the hydrogen*

The reactivity of enamides is very different from that of the corresponding enamines <sup>5</sup>. In many cases where enamides reacted it was evident that the nitrogen lone pair was largely delocalised within the amide

portion of the molecule <sup>6</sup>. It was therefore of interest to determine whether the regioselectivity of the attack by the hydride equivalent is the same as with an enamine.

In a first experiment D<sub>2</sub>O was used instead of H<sub>2</sub>O in the treatment of the reaction mixture of **2a** with **1a**. This method failed to provide incorporation of deuterium in **3**. It can be assumed that a proton was abstracted from the solvent by the strong carbanion formed in the first step of the reaction <sup>7</sup>. This hypothesis was confirmed by performing the reaction in CD<sub>3</sub>CN (99.6 % in deuterium) and treatment of the reaction mixture with D<sub>2</sub>O. A mixture of the two compounds **3a** (40 %) and **3a''** (X = H, Y = D: 60 %) was thus obtained in 85 % chemical yield. With a view to confirming the site of attack of the hydrogen, we synthesized the deuterated model **1b** using the reduction/oxidation/reduction procedure described by Kaminsky with simpler NADH models <sup>8</sup>.



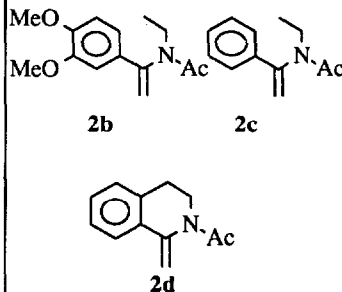
The reduction of **2a** with reagent **1b** gives **3a'** (X = D, Y = H) in 50 % chemical yield and with deuterium incorporation of 85 % determined by 200 MHz <sup>1</sup>H NMR spectroscopy (Scheme 1; the remaining **2a** was recovered). The introduction of the deuterium atom to the  $\alpha$  position of the ethylenic bond suggests that the regioselectivity of the hydride equivalent issued from **1b** is governed by the nitrogen lone pair of the enamide structure. But in this hypothesis the case of the reduction of **2a** with **1b** is a surprise compared to previously reported results <sup>3,5,9</sup> and to the behaviour of enamines which are reduced with hydride reagents only in the presence of protons <sup>10</sup>.

Reduction of a substrate with an NADH model is in nearly almost all cases mediated with the presence of magnesium ions <sup>11</sup>. In the case of **1a** or **1b**, it can be assumed that the substrate is activated by the "acidic" character of the catalyst. It can also be suggested, that the reduction occurred through a multistep mechanism involving an initial electron transfer process <sup>11a</sup>. The ease of the reaction could be related to the reactivity of enamides in the excited state <sup>5</sup>.

#### Reductions of various enamides :

The reductions of substrates **2a**, **2b**, **2c** and **2d** performed with **1a** gave the results reported in the following table.

entry	Starting substrate <b>2</b>	Reduction product yield (%)
1	<b>a</b>	90
2	<b>b</b>	0
3	<b>c</b>	0
4	<b>d</b>	27

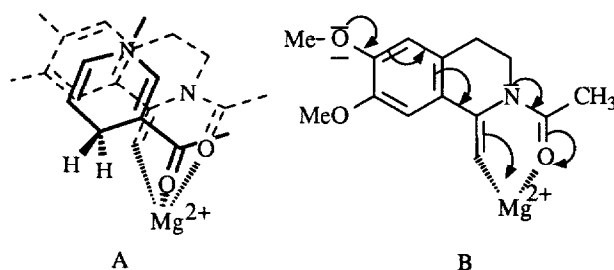


Typical procedure : the reactions were performed under an argon atmosphere with 1 mmol of **1a**, 0.7 mmol of substrate (**2a,b,c,d**) and 1 mmol of anhydrous magnesium perchlorate in dry acetonitrile (5 ml). The mixture was stirred at 60 °C, in the dark, for 3 days. After cooling, the mixture was treated with 3 drops of water, then a small amount of silica (silica SI amicon 60 Å ref 84086) was added and the solvents removed. The resulting cake was incorporated on the top of a silica column and eluted with ethyl acetate. The reduction product was first eluted. The reactions were performed several times and when no reduction occurred, the starting material was recovered. In the case of **2d** with a 5 fold excess in **1a** the yield in **4d** was only 33 %. The starting **2d** was recovered but no **1a** was recovered.

As can be seen (entries 1 and 4) only the cyclic enamides **2a** and **2d** were reduced<sup>12</sup>. This behaviour can be related to the carbonyl i.r. absorption which appears at 1630 cm<sup>-1</sup> for **2a** and **2d** and at 1660 cm<sup>-1</sup> for **2b** and **2c**. This indicates that the conjugation of the carbonyl group with the lone pair of the nitrogen atom in **2a** and **2d** is very much more efficient than in **2b** and **2c** certainly for geometry reasons. Moreover, and as already mentioned, the reaction occurs in the presence of magnesium ions which are involved in the activation of the substrate and also in a ternary complex built with the substrate and the reagent<sup>11a</sup>. In the case of cyclic enamides **2a** and **2d** the ethylenic double bond and the carbonyl function are probably ideally located for chelation with Mg<sup>2+</sup> to ensure the efficient transfer of the hydrogen as can be seen in scheme A. The oxygen atom of the enamide carbonyl probably plays an important role as already mentioned in catalytic reduction of these substrates<sup>13</sup>.

In the case of non cyclic substrates **2b** and **2c** the free rotation around the C<sub>α</sub>-N bond of the enamide disfavours this ideal location. Moreover the carbonyl of the enamide is less conjugated with the nitrogen lone pair and this phenomenon disfavours the ability of the oxygen atom to chelate with magnesium ions.

Finally, the highest reactivity of **2a** compared to **2d** (yield 90 % instead of 27 %) can be a consequence of the high electron donor effect of the methoxy groups in **2a** which reinforces the electronic density of the ethylenic double bond and as a consequence its ability to coordinate with magnesium ions (B).



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