Pergamon

Tetrahedron Vol. 50, No. 46, pp. 13135-13144, 1994
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0040-4020/94 $7.00+0.00

0040-4020(94)00846-9

Reduction of New Substrates with a NADH Model Reduction of N-acyl-enamines: Mechanism and Scope

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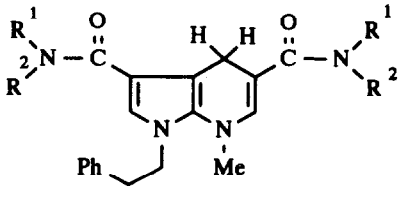
Abstract: Several examples of the successful reduction of N-acyl-enamine derivatives with a NADH model in the pyrrolo[2,3-b]pyridine series are given. It is shown, that the reduction is strongly dependent on electronic and geometrical factors. It appears that, in general, the success of the reduction can be related to the ability of the magnesium ions to form a complex with the acyl group and with the enamine function. Herein the reduction of the enamine function in α-acetylaminoacrylate derivatives is discussed from this point of view and the influence of the enamine ⇆ imine equilibrium is discussed.

INTRODUCTION

A few years ago we reported the synthesis and the use of NADH models in the pyrrolo[2,3-b]pyridine series. The main role of the annulated pyrrole ring was to protect the 5,6-double bond of the 1,4-dihydronicotinamide ring against side reactions essentially caused by traces of water and to increase the reactivity of the model. According to their synthesis, these reagents contain two carboxamides functions, i.e., one at the pyrrole ring and the other at the 3 position of the 1,4-dihydropyridine ring.[1]

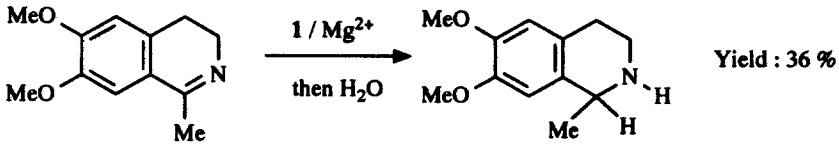


1: $R^1, R^2 = Et$

2: $R^1 = H$; $R^2 = —\overset{*}{C}H(S)-CH_2Ph$ CH_2OH

Figure 1

Reagents **1** and **2** showed a high reactivity towards many substrates.[2] With reagent **1**, we investigated the reduction of imines such as **3** with a view to obtaining salsolidine which is an important alkaloïd.

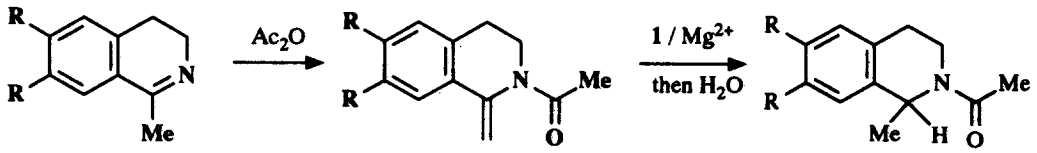


3 **4: (±) salsolidine**

Scheme 1

The chemical yield was only 36 %. This result was a little surprising, as there are several reports of the successful reduction of imines with various NADH models.[3,4,5]

Reductions with NADH models are generally performed in the presence of magnesium ions, which are implicated in a ternary complex: model/Mg^{2+}/ substrate.[6,7] This complex plays a fundamental role in the hydrogen transfer between the reagent and the substrate through complexation of the two partners with the metal ions. The poor result obtained in the reaction depicted in scheme 1, could be due to the low ability of the reaction partners to build a suitable ternary complex. This led us to modify substrate **3**, by transforming the imine function into a N-acyl-enamine function where the acyl moiety could be suitable for complexation with magnesium ions.



5 : R = OMe — **5** → **5'** Yield 95 % — **5'**: R = OMe

6 : R = H — **6** → **6'** Yield 27 % — **6'**: R = H

Scheme 2

In a preliminary report [8] we described the high yield obtained in the reduction of **5** with **1** (95%) and we showed that the hydrogen atom issued from **1** was transferred at the α carbon of the N-acetylenamine structure. It was assumed that the crucial factor was the ability to form a ternary complex, involving the pi-system of the carbonyl group of the reagent **1** and the N-acyl-enamine function of the substrate (Fig 2).

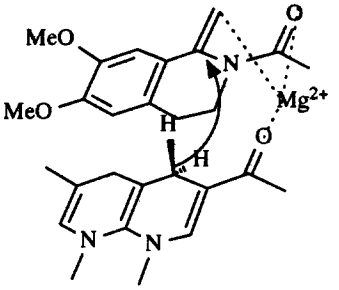


Fig 2

Moreover, it was shown that the presence of the electron-donating methoxy groups on the benzene ring, favours the reaction (The yield in reduction of **6** was only 27 % as can be seen on Scheme 2).

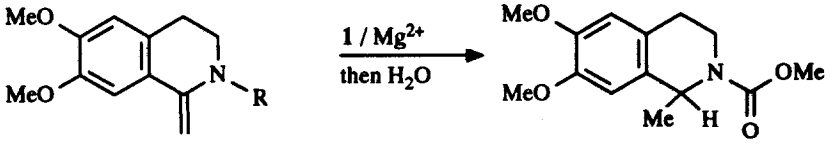
In the literature there are several reports of the efficient reduction of such substrates by hydrogen, in the presence of a catalyst.[9,10,11] However, to our knowledge, there is only one report of the reduction of a N-acyl-enamine by an hydride donor.[12]

The aim of this paper is to put forward more refined arguments for the hypothesis depicted in Fig 2 and to study the reduction of the enamine function in various N-acyl-enamines structures with a view to obtaining information: 1) on the role of the N-acyl function; 2) on the role of the geometry of the substrate ; 3) on the resemblance with the reduction of the parent imines; and 4) on the reduction of the enamine group in α-acetylaminoacrylate derivatives.

RESULTS AND DISCUSSION

I) Reduction of substrates 5, 7 and 8 : role of the N-acyl function.

1) Results. As Mg^{2+} ions probably play a crucial role in the reactivity of **5**, it was of interest to study substrates **7** and **8**, where the electronic effects of the methoxy and trifluoromethyl groups are opposite. These substrates were prepared by a similar procedure as that used for **5** [13] and underwent reduction, with reagent **1**, under usual conditions (model/substrate/Mg^{2+} : 1/1/1, at 60°C, in CH_3CN as the solvent).



7 : R = COOMe — With **7** : Yield 95 % in **7'**

7a : R = Me — With **7a** : degradation products

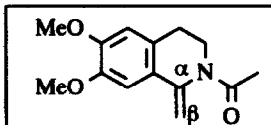
8 : R = $COCF_3$ — With **8** : no reaction

Scheme 3

It can be seen on Scheme 3 that the reduction of **8** failed while the reduction of **7** (total reduction in 5 h) was easy, compared to that of **5** (total reduction in 20 h).

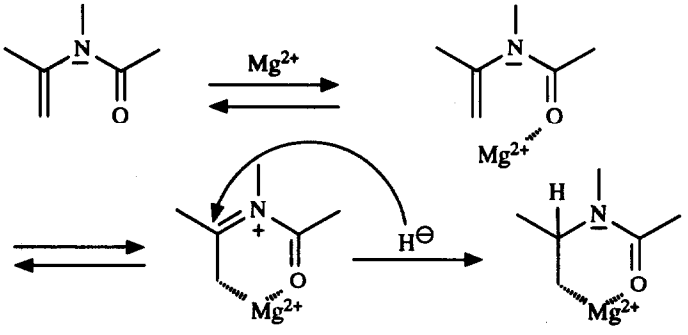
2) NMR study. ^{13}C NMR spectroscopy is a valuable method for obtaining information concerning the complexation of magnesium ions with a substrate or with an NADH model.[14,15,16] We recorded the spectra of compounds **5**, **7** and **8** in CD_3CN with 1 equivalent of Mg^{2+} and without Mg^{2+}. The values are reported in Table 1.

Table 1: ^{13}C NMR spectra of compounds **5**, **7** and **8**. $\Delta\delta = \delta$ with Mg^{2+} -δ without Mg^{2+}.

	with Mg^{2+}			without Mg^{2+}			Δδ		
	5	7	8	5	7	8	5	7	8
Cα	142.7	139.9	-	143.8	140.9	142.0	-1.0	-1.0	-
Cβ	107.4	104.9	107.1	104.8	102.6	107.1	2.6	2.3	0.0
CH_2-N	43.7	44.8	45.5	42.5	44.5	45.5	1.2	0.3	0.0
C=O	172.3	156.4	155.5	169.6	155.9	155.8	2.8	0.5	-0.3
OMe	-	54.7	-	-	53.2	-	-	1.5	-

3) Discussion. As postulated above the ethylenic double-bond of compounds **5** and **7** is undergoing complexation with Mg^{2+}, since there are modifications of the δ on Cα and Cβ. Compound **8** seems to be little affected. Moreover an I.R. study showed that the C=O frequency of **5** is shifted considerably by the presence of Mg^{2+} (1652 cm^{-1} with Mg^{2+} and 1600 cm^{-1} without Mg^{2+}) and in the case of **8** there is no noticeable variation (1693 and 1685 cm^{-1}). We'll first discuss the chemical shifts: It was observed that the reduction of **7** was very much faster than the reduction of **5**. If one compares the chemical shift of Cβ in compounds **5** and **7** without Mg^{2+} i.e. 104.8 and 102.6 ppm respectively, it can be seen that the most shielded carbon is Cβ in compound **7**. So it seems that the electron density is higher at Cβ in compound **7**, a phenomenon which assumes the involvement of this carbon in the formation of the bidentate complex represented on Figure 2. On the other hand the reduction of compound **6** resulted in a lower yield than that of compound **5** (Scheme 2). This result can be related to the δ of Cβ in **6** (106.8 ppm) which shows that the electron density at this carbon is lower than the electron density at Cβ in **5**. This behaviour probably hinders the formation of the bidendate structure in the case of **5**.

We'll now discuss the observed Δδ on various carbon atoms: in the case of **5** or **7**, Cα is shielded and Cβ and C=O are deshielded. It can be assumed that Mg^{2+} is involved in complexation with the carbonyl groups of compounds **5** and **7**, and with the lone pair of the nitrogen atom, leading to a partially positively charged atom which could explain the shielding of Cα and the deshielding of Cβ. This behaviour can be compared with the mechanism proposed for the reduction of an enamine with a hydride donor under protic conditions : protonation → enaminium cation then tautomerism to an iminium structure and attack by a hydride.[17] In our case a similar behaviour can be envisaged, leading to the following mechanism :



Scheme 4

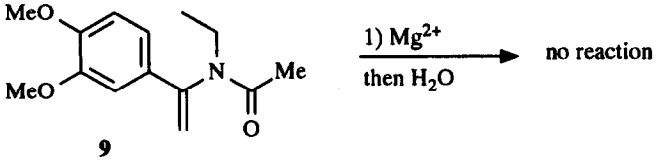
Owing to this proposal two consequences occur : 1) the enamine function is activated towards nucleophilic attack with the hydride equivalent and this attack would occur normally at Cα. 2) the complexation of the substrate in a bidentate structure allows the formation of an "ideal" ternary complex between reagent **1**, Mg^{2+} and the substrate as represented in Figure 2. The complexation of the π system of an ethylenic double bond, with a metal ion is often mentioned in catalytic reductions.[18,19,20] A modeling study (PC model method) showed that, in the case of substrates **5** and **7** the C=C and C=O system are almost coplanar, a behaviour which facilitates the occurence of a bidentate system involving these two groups.

Finally, it can be assumed that the ability of the acyl function linked to the nitrogen atom to establish a complexation with Mg^{2+} is the crucial starting point for a sequential process, leading to the reduction of the substrate. In this way it can be seen that the high electron-withdrawing effect of the CF_3 group hinders the complexation of the C=O group of **8** with Mg^{2+}.

Note: An experiment was performed with substrate **7a** (Scheme 3) having no acyl function at the nitrogen atom with a view to estimate the role of the acyl function. The reduction of **7a** with model **1** in the presence of Mg^{2+} gave a very small amount of reduction product together with a large amount of degradation products.

II) Reduction of substrate 9 : role of the cyclized structure.

Small structural modifications (i.e., absence of methoxy groups in **6**) cause a large variation of reactivity of a substrate towards reagent **1**. So we decided to study substrate **9**, where the rigid structure encountered in the cyclized compound **5** was suppressed. The reduction of this substrate failed despite prolonged reaction time and the use of excess reagent **1**.



9

Scheme 5

This apparently surprising result can be explained by comparing the ^{13}C NMR spectra of compounds **5** and **9**.

Table 2: Chemical shifts of Cα, Cβ and C=O in compounds **5** and **9**.

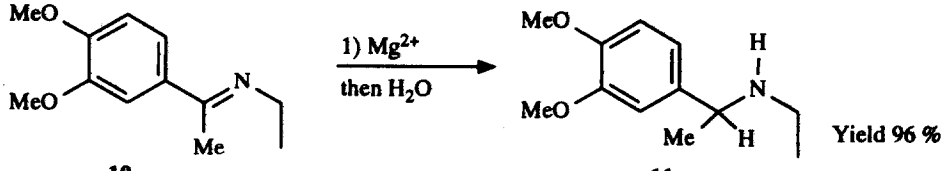
	with Mg^{2+}		without Mg^{2+}		Δδ	
Position	**5**	**9**	**5**	**9**	**5**	**9**
Cα	142.7	145.2	143.8	147.4	-1.1	-2.2
Cβ	107.4	113.7	104.8	112.7	2.6	1.0
C=O	172.3	173.5	169.6	170.6	2.7	2.9

The main feature is that Cβ in **9** appears at low field compared to Cβ in **5** (δ = 112.7 instead of 104.8 without Mg^{2+}). However Mg^{2+} ions seem to undergo complexation with the carbonyl function in **5** and **9** as can be seen on the Δδ (2.7 and 2.9 ppm). So it appears that in **9** the second step did not occur. This behaviour is probably a consequence of the large dihedral angle between the aromatic ring and the plane of the ethylenic double bond as observed using molecular modeling softwares (PC model method). This behaviour can be attributed to the free rotation around the ring and the Cα in the non-cyclized substrate **9**. So, the electron-donating effect of the ring group does not influence the Cβ. Consequently this carbon does not possess a sufficient electron density to insure the complexation of Mg^{2+} in the second step of the mechanism proposed in Scheme 4. This assumption is confirmed by the low Δδ observed on Cβ of

compound **9** compared to that Cβ observed for Cβ of compound **5**.

III) Reduction of imine 10.

Another surprising result was obtained during the reduction of imine **10**, a precursor of **9**, with reagent **1**. The yield of amine **11** was 96 % which is very much higher than the yield obtained (36 %) during the reduction of the cyclized analog **3** (Scheme 1).

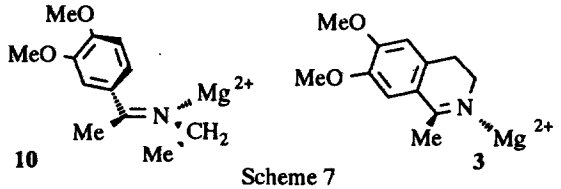


10 **11**

Scheme 6

The previously reported reductions of imines by NADH models show that the best results are obtained with non-cyclized structures and that activation of the imine by a Lewis acid (proton, silica or Mg^{2+}) was necessary.[3,4,5] In our case, and in similar cases in the literature, imines derived from aryl ketones or aryl aldehydes are easily reduced in the presence of Mg^{2+}. However, the carbonyl precursors are not reduced under the same conditions, despite the fact that the intrinsic reactivity of an imine towards a nucleophilic species such as a hydride equivalent, is significantly lower than the reactivity of the parent ketone or aldehyde.

An NOE experiment showed that imine **10** has an anti configuration. It can be asumed that in the ternary complex the complexation of the imine with a magnesium ion results in steric hindrance, which causes a deconjugation of the C=N bond and the aromatic ring. This behaviour cannot occur with the cyclized analog **3**. As a consequence the former substrate would be more reactive than the latter (Scheme 7).

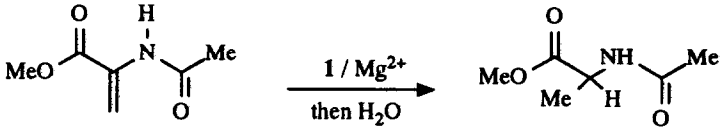


10 **3**

Scheme 7

IV) Reduction of amino acids precursors.

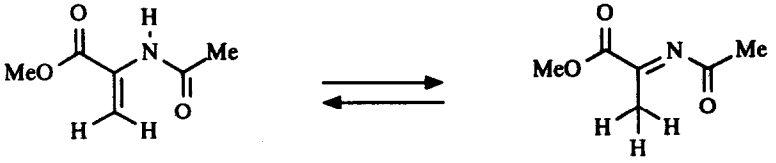
Some of the above results suggest that in the N-acyl-enamine series the reactivity of the enamine function is largely influenced by the complexation of Mg^{2+} with the β carbon and with the carbonyl function. This behaviour prompted us to study the reduction of substrate **12**, [21] leading to **13**, a precursor of (±)-alanine.



12 **13**

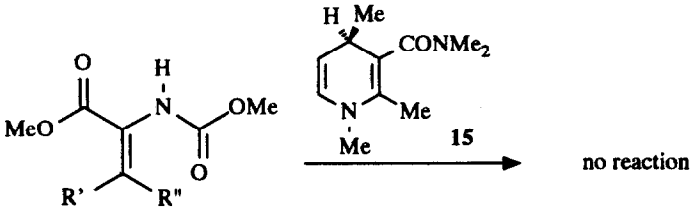
Scheme 8

The amino acid precursor **13** was obtained in a 100 % yield. Substrate **1** is, to our knowledge, the first example of the successful reduction of this type of substrate with an NADH model. The ease of this reduction can be explained by two hypotheses : 1) The reduction occurs through the enamine structure **12a** (Scheme 9). A spectroscopic study showed that the C=C double bond is involved in complexation with Mg^{2+} ($\Delta\delta$ on Cβ : 6.85 ppm and on Cα : -1.2 ppm). So a bidendate structure occurs to help the formation of the ternary complex as with substrates **5**, **7** and **8**. 2) The reduction could occur through the tautomeric imine form **12b** (Scheme 9).



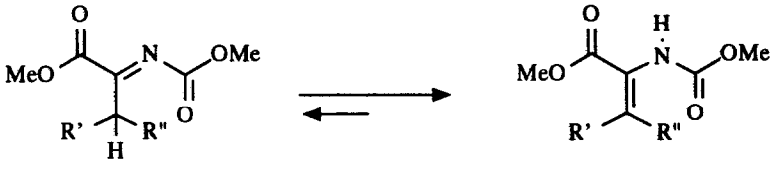
12a Scheme 9 **12b**

This behaviour is suggested in the tentative reduction of **14a** with the (*N*,*N*)-1,2,4-pentamethyl-1,4-dihydronicotinamide derivative **15**.[22]



14a Scheme 10

This failure was attributed to the fact that the N-acyl-enamine structure is the more stable tautomeric form of the imine compound.

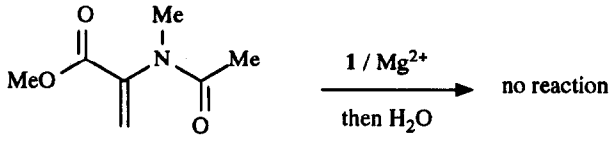


reduced not reduced

14b Scheme 11

The enamine **14a** would be unreactive towards reagent **15**. This argument was supported by the fact that non-tautomerizable substrates similar to **14b** where the hydrogen atom between R' and R" was replaced by a bromine atom could be reduced.

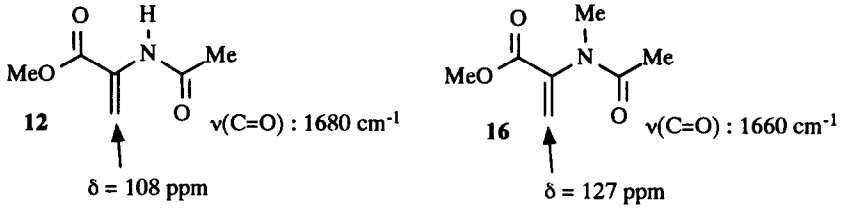
The ^1H NMR spectrum of **12**, in $CDCl_3$ shows that it essentially exists under the enamine form without or with Mg^{2+} ions, even in the presence of model **1** (integration 3,3,2 and 1 in **12a** instead of 3,3 and 3 in **12b**). We performed an experiment with the non-tautomerizable substrate **16**. The reduction failed, even after prolonged reaction time or addition of excess Mg^{2+} ions (Scheme 12). Substrate **16** was recovered.



16

Scheme 12

A spectroscopic study of substrates **12** and **16** showed two main features : 1) the IR absorption of the carbonyl linked to the nitrogen in **16** occurs at a lower frequency than in **12** (1660 cm^{-1} instead of 1680 cm^{-1}). This means that the conjugation between the nitrogen lone pair and the carbonyl function is probably better in **16**. As a consequence the availability of the lone pair for the carbon-carbon double bond is low. 2) the NMR spectra show that Cβ in **16** is much more deshielded than the corresponding atom in **12** (δ : 127 ppm instead of 108 ppm). This means that the carbon carbon double bond in **16** is essentially influenced by the electron-withdrawing effect of the ester function. The electron density at Cβ is therefore not sufficient for the creation of the bidentate structure.



Scheme 13

Moreover, it is probable that the steric hindrance, often observed with tertiary amides, [23] caused by the additional methyl group at the nitrogen hinders the coplanarity between the C=C and the C=O, a behaviour which is reinforced by the presence of Mg^{2+}. As a consequence, the creation of the bidendate structure is impossible and reduction cannot occur. This argument may be suggested to explain the failure of the reduction of **14a** with **15** : the substituents R' and R" hinder the coplanarity between the C=C and the C=O and hence disfavour the formation of a bidendate structure.

Finally, it appears that the reduction of N-acyl-enamine derivatives, with reagent **1** is very sensitive to electronic or geometrical effects. It seems that the main factor is the formation of a bidendate structure, wherein Mg^{2+} is involved together with the acyl function and the carbon-carbon double bond. Chelation is fundamental for the success of the reduction and some minor modifications can lead to major differences in the results obtained.

EXPERIMENTAL

The infra-red spectra were recorded on a Beckman IR 4250 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz or on a 400 MHz Brucker apparatus. Spectra were recorded in deuteriochloroform or in deuterioacetonitrile. Reagents **1** and **2** were synthesized as previously described in the literature.[1,2]

Synthesis of substrates.

3,4-Dihydro-6,7-dimethoxy-2-methylisoquinoline: 3. This compound was obtained from N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide.[24]

2-Acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline: 5. Obtained from **3** by treatment with acetic anhydride in the presence of pyridine.[24]

2-Acetyl-1-methylene-1,2,3,4-tetrahydroisoquinoline: 6. This compound was obtained from N-(2-phenylethyl)acetamide.[25]

Methyl 6,7-Dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline-2-carboxylate: 7. Compound **3** (2.70 g, 0.013 mol) and 1.93 g (0.019 mol) of triethylamine were dissolved in dichloromethane (50 ml). A solution of 1.66 g (0.018 mol) of freshly distilled methyl chloroformate in dichloromethane (3 ml) was added dropwise. The mixture was warmed to reflux for 3 hours. After cooling the organic phase was washed with water (3x10 ml), dried and the solvent evaporated off. This compound was washed with hot diethyl ether and purified by flash chromatography (silica gel , ethyl acetate, R_f = 0.9). Yield 90 %. m. p. = 94 °C. ^{1}H NMR ($CDCl_3$): 7.10 (s,1H); 6.58 (s,1H); 5.52 (s,1H); 5.35 (s,1H); 3.89 (s,3H); 3.87 (s,3H); 3.84 (t,2H); 3.77 (s,3H); 2.82 (t,2H). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.57; N, 5.32 %. Found: C, 63.5; H, 6.6; N, 5.2 %.

2-Trifluoroacetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline : 8. Compound **3** (1.64 g, 0.008 mol) and 0.8 ml (0.01 mol) of pyridine in dichloromethane (25 ml) were cooled at -50°C. A solution of 1.36 ml (0.001 mol) of trifluoroacetic anhydride in dichloromethane (6 ml) was added, and the mixture left for 3 hours at -50°C. The mixture was allowed to reach room temperature, and then water was added, the organic phase dried and the solvent evaporated off. The compound was purified by flash chromatography (silica gel, CH_2Cl_2, R_f = 0.6). Yield 69 %. m. p. = 80 °C. ^{1}H NMR ($CDCl_3$): 7.20 (s, 1H); 6.60 (s, 1H); 5.61 (m, 1H); 5.24 (m, 1H); 3.94 (t, 2H); 3.9 (s, 3H); 3.88 (s, 3H); 2.95 (t, 2H). Anal. Calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.65; N, 4.68 %. Found C, 56.0; H, 4.4; N, 4.5 %.

N-[1-(3,4-Dimethoxy)phenylethylidene]ethylamine: 10. This compound was obtained from condensation between the appropriate ketone and ethylamine. Ethylamine (6 ml, 0.092 mol) was cooled at 0°C. A solution of 3,4-dimethoxyacetophenone (3 g, 0.017 mol) in anhydrous ether (15 ml) was added under argon. A solution of titanium tetrachloride (1,5 ml, 0.014 mol) in hexane (14 ml) was added dropwise. The mixture was stirred for one hour at 0°C, then for one hour at room temperature. The solid was filtered and the solvent evaporated off. Yield 80 %. m. p. < 50°C. ^{1}H NMR ($CDCl_3$): 7.2 (m, 3H); 3.95 (s, 3H); 3.90 (s, 3H); 3.55 (q, 2H) ; 2.2 (s, 3H) ; 1.3 (t, 3H). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 69.6; H, 8.2; N, 6.7 %. Found C, 69.0; H, 8.9; N, 6.4 %.

N-Ethyl-N-[1-(3,4-dimethoxy)phenylvinyl]acetamide: 9. Compound **10** (1g, 0.005 mol) and triethylamine (0.8 ml, 0.006 mol) were dissolved in dichloromethane (7 ml) and the mixture cooled at 0°C. A solution of acetyl chloride (0.41 ml, 0.006 mol) in dichloromethane (3 ml) was added dropwise. The mixture was stirred for one hour. The organic phase was washed with water (3x5 ml), dried and the solvent evaporated off. The product was purified by flash chromatography (Silicagel, CH_2Cl_2/Et_2O: 80/20). F = 66 °C. ^{1}H NMR ($CDCl_3$): 7.00 (s, 3H); 5.70 (s, 1H); 5.10 (s, 1H); 3.95 (s, 6H); 3.55 (q, 2H); 2.10 (s, 3H); 1.25 (t, 3H). Anal. Calcd for $C_{14}H_{19}NO_3$: 67.45; H, 7.68; N, 5.62 %. Found C, 67.0; H, 7.8; N, 5.4 %.

Methyl 2-Acetamidoacrylate: 12. To a suspension of 2-acetamidoacrylic acid (2.58 g, 0.02 mol) and sodium hydrogenocarbonate (3.36 g, 0.04 mol) in dimethylformamide (50 ml), was added a solution of methyl iodide (10 ml) in dimethylformamide (20 ml). The mixture was stirred for 36 hours. The solvent was distilled off and water (10 ml) was added. The product was extracted with dichloromethane (3x8 ml), the organic phase dried and the solvent evaporated off. The compound was purified by flash chromatography (Silica gel, cyclohexane /ethyl acetate: 1/1). Yield 84 %. m. p. = 54°C. ^{1}H NMR ($CDCl_3$): 7.85 (s, 1H); 6.35 (s, 1H); 5.90 (s, 1H); 3.85 (s, 3H); 2.15 (s, 3H). Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H : 6.34; N, 9.78 %. Found: C, 51.0; H, 6.4; N, 9.8 %.

Methyl 2-(*N,N*)-Acetylmethylaminoacrylate: 16. A mixture of 2-acetamidoacrylic acid (1.29 g, 0.01 mol), silver oxide (9.27 g, 0.04 mol) and methyl iodide (6 ml) in dimethylformamide (30 ml) was stirred for 36 hours. The solvent was evaporated off and the product purified by flash chromatography (Silica gel, cyclohexane / ethyl acetate: 60/40). Yield : 71 %. The product was not analytically pure. ^{1}H NMR ($CDCl_3$): 6.3 (s, 1H); 5.7 (s, 1H); 3.8 (s, 3H); 3.1 (s, 3H); 2.0 (s, 3H).

Typical procedure for the reduction of a substrate.

A mixture of substrate (1 mmol), model (1.1 mmol) and magnesium perchlorate (1.1 mmol) in

acetonitrile (5 ml), degassed with argon was stirred for 3 days at 60°C, under argon and in the dark. Water (3 drops) was added and the solvent evaporated off. The mixture was purified by flash chromatography.

For substrates **3** and **10** : 1M hydrochloric acid (5 ml) was added to the mixture. The aqueous phase was washed with ethyl acetate and then neutralised with a sodium carbonate 1M solution. The product was extracted with ethyl acetate. The organic phase was dried and the solvent evaporated off.

Reduction of 5: The crude reduction product was chromatographed on silica gel with ethyl acetate (R_f = 0.3). The yield in **5'** was 95 %. ^1H NMR ($CDCl_3$): 6.60 (s, 1H); 6.56 (s, 1H); 5.58 (q, 0.6H); 4.87 q, 0.4H); 3.84 (s, 3H); 3.83 (s, 3H); 3.65 (m, 2H); 2.82 (m, 2H); 2.17 (s, 1.2H); 2.15 (s, 1.8H); 1.52 (d, 1.2H); 1.43 (d, 1.8H).

Reduction of 6: The mixture of **6** and **6'** was chromatographed on silica gel with ethyl acetate (**6**: R_f = 0.7 and **6'**: R_f = 0.4). The yield in **6'** was 27 %. ^1H NMR ($CDCl_3$): 7.17 (s, 4H); 5.65 (q, 0.6H); 4.93 (q, 0.4H); 3.67 (m, 2H); 2.87 (m, 2H); 2.18 (s, 1.2H); 2.15 (s, 1.8H); 1.53 (d, 1.2H); 1.43 (d, 1.8H)

Reduction of 7: The crude reduction product was chromatographed on silica gel with ethyl acetate (R_f = 0.6). The yield in **7'** was 95 %. ^1H NMR ($CDCl_3$): 6.5 (s, 2H); 5.05 (m, 1H); 3.75 (s, 6H); 3.65 (s, 3H); 3.2 (m, 2H); 2.6 (m, 2H); 1.35 (d, 3H).

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(*Received in Belgium* 18 *July* 1994; *accepted* 8 *September* 1994)