Hydrogenation of β-N-Substituted and β-N,N-Disubstituted Enamino Esters in the Presence of Iridium(I) Catalyst

Hania Hebbache, Zakia Hank, Christian Bruneau, Jean-Luc Renaud

Abstract: Several new β-amino esters were prepared in two simple steps from β-keto ester derivatives and primary and secondary amines under mild conditions. The hydrogenation of various enamino esters was performed at 50 °C in the presence of iridium catalysts. The new β-N-substituted amino esters were isolated in high yields.

Key words: catalysis, hydrogenation, iridium, β-amino esters

β-Amino acid derivatives are building blocks of choice for the preparation of β-peptides. These types of peptides usually present high enzymatic stability and three-dimensional structures of interest. Some β-amino acids themselves are biologically active products, for instance cis-pentacine shows high antibiotic and antifungal activities, and emeriamine exhibits hypoglycemic and antiecetogenic properties (Figure 1). A variety of polyfunctional linear products, as well as macrocycles incorporating β-amino acid substructures have revealed interesting biological activities (Figure 1).

The preparation of such β-amino acid derivatives in optically pure form has become a challenge for organic chemists in recent years. The main approaches for stereoselective synthesis of β-amino acids are based on homologation of α-amino acids, enzymatic resolution, enolate addition to imines, Curtius rearrangement, conjugate addition of nitrogen nucleophile to α,β-unsaturated derivatives, aminohydroxylation, and β-lactam synthesis. However, the most promising method for a large scale preparation of optically pure β-amino acids appears to be the catalytic asymmetric hydrogenation of β-acetamidoacrylates, which involves clean atom economical reactions and offers the preparation of both R- and S-enantiomers. Most of the current approaches required an N-acyl or N-carbamoyl protecting groups on the β-dehydroamino acids to achieve high enantioselectivities, via a chelation between the substrate and the metal. But the major drawback of this strategy was the difficulty to protect and remove this protecting-chelating group. To avoid these extra steps, one solution might be either the enantioselective hydrogenation of β-N-alkyl- or β-N-aryl-enamino esters or a direct reductive amination. After the evidence that enamines could be hydrogenated by transi-
tion metal complexes, the first enantioselective hydrogenation of unprotected enamino esters was reported by the Merck group in 2004. In 2005, Zhang reported the hydrogenation of β-N-arylenamino esters in the presence of a catalytic amount of Rh-Tangphos in TFE at 50 °C. The first and up to date only, direct reductive amination was reported by the Lanxess and the Takasago groups. The chiral β-amino esters were obtained in a one-pot synthesis from β-keto esters and ammonium acetate under a pressure of hydrogen in the presence of a ruthenium catalyst bearing a Josiphos type optically active ligand. From acyclic β-keto esters, the chemoselectivity in favor of the amino ester and the enantioselectivity were excellent, from acyclic β-keto ester the chemoselectivity in favor of the amino ester was still high, but the diastereo- and the enantioselectivity were moderate.

Finally, in the literature, no general report on hydrogenation of β-N-substituted enamino esters was described. We report here a general procedure for the synthesis of a wide range of β-N-substituted amino esters via a catalytic hydrogenation of β-N-substituted enamino esters under mild conditions.

We recently described the synthesis of various β-N-substituted enamino esters and β-N,N-disubstituted enamino esters based on a simple condensation of a primary or a secondary amine with β-keto esters in the presence of a Lewis acid. We have extended this study to several substituted anilines leading to the formation of the enamino esters. Whatever the substituents on the aromatic ring and the β-keto esters used, the yields are good (73–97%, see experimental section). It is worth to mention that using this procedure, only the Z-β-N-substituted enamino esters were isolated from the condensation of a primary amine with a β-keto ester, and only the E-β-N,N-disubstituted enamino esters resulted from the condensation of a secondary amine (Scheme 1).

The direct hydrogenation of these substrates was investigated with transition-metal catalysts. As they demonstrated good efficiency in the hydrogenation of β-acetamidoacrylates, [Rh(diphosphine)(cod)]BF₄ rhodium complexes were used as precatalyst in our first attempts. No reaction was observed in methanol or in the more acidic trifluoroethanol at 50 °C under 10 bar of hydrogen starting from methyl 3-N-benzylaminobut-2-enoate (3a) and methyl 3-pyridinobut-2-enoate (3b). Even an increase of the catalyst loading (from 1 to 5 mol%) did not improve the reactivity. Under the same reaction conditions, ruthenium complexes, such as [Ru(p-cymene)(diphosphine)Cl]Cl and RuClCp(diphosphine), did not provide any hydrogenated products either.

However, in the presence of the iridium complex [Ir(P(OPh)₃)₂(cod)]PF₆, either in trifluoroethanol or in

Scheme 1

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methanol as solvent, at 50 °C for 20 hours under 15 bar of hydrogen, 3a was hydrogenated to methyl 3-N-benzylaminobutan-2-0ate (4a) in moderate yield (50%). A rapid screening of iridium catalysts demonstrated that the simple [IrCl(cod)]2 iridium precursor at 50 °C under 15 bar of hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2). The nature of the solvent had a strong influence on the reactivity; alcohols (such as methanol or trifluoroethanol), and THF did not lead to complete hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation, whereas in CH2Cl2 full conversion was reached. The hydrogen pressure is also crucial for this hydrogenation; below 10 bar of hydrogen in dichloromethane, the reaction did not go to completion. Thus, hydrogen led to the saturated amino ester in good yield (Scheme 2).

With these conditions, the scope of the hydrogenation reaction was evaluated for a variety of β-N-substituted enaminoesters (Table 1). In all reactions, whatever the N-alkyl substituent, the conversions were complete and isolated yields of products were almost quantitative. Except for enamino ester 3j, the hydrogenation occurred rapidly (<3 h). The lower reactivity of 3j might be due to the conformation of the enamino double bond with the aromatic substituent at C-3.

Starting from N-aryl-substituted enamino esters, conversions were complete and isolated yields were almost quantitative (superior to 95% after purification on silica gel chromatography in all the following examples). As compared to the alkyl series, the enamino esters 3k–s were less reactive and hydrogenations took usually longer reaction times. The nature and the position of the substituent on the aromatic ring had no noticeable influence on the reactivity (Table 2, entries 5–9).

With secondary enamino esters 3t,u, the hydrogenation proceeded also efficiently. As observed with the previous enamino esters 3a–s, in methanol or mixture of MeOH–CH2Cl2 the reaction was slower than in CH2Cl2. Then, in methanol after 6 or 16 hours, the reaction was not completed, whereas in CH2Cl2, the amino esters 4t,u were isolated in 98 and 99% yield, respectively, within 4 hours under 10 bar of hydrogen (Scheme 3).

### Table 1 Hydrogenation of 3-N-Alkylamino Esters 3a–j

<table>
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<th>Entry</th>
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* The hydrogenation reactions were carried out with 0.5 mmol of enamino ester 3a–j and 1% of [IrCl(cod)]2 precatalyst in 5 mL of CH2Cl2.

* Amount of catalyst used: 2 mol%.

### Table 2 Hydrogenation of 3-N-Arylamino Esters 3k–s

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<th>Entry</th>
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<td>4s</td>
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* The hydrogenation reactions were carried out with 0.5 mmol of enamino ester 3a–j and 1% of iridium precatalyst in 5 mL of CH2Cl2.

* Amount of catalyst used: 2 mol%.

We then investigated two phosphoramidites L1 and L2 (Figure 2), which were recently introduced as efficient chiral ligands for a number of reactions, in the hydrogenation of the enamino ester 3a. After a screening of solvent
(MeOH, THF, CH₂Cl₂, i-PrOH, toluene, EtOAc), pressure (10, 20, 30 bar) and temperature (40, 50, 60, 70 °C), we found that using 1 mol% of previously prepared catalyst [Ir(cod)L₁Cl] or [Ir(cod)L₂Cl] the amino ester 4a was obtained quantitatively at 70 °C in THF under 10 bar of hydrogen, but as a racemic mixture.

In conclusion, we have found a general procedure for the synthesis of a wide range of new β-N-substituted and β-N,N-disubstituted amino esters via catalytic hydrogenation of β-N-substituted and β-N,N-disubstituted enamino esters under mild conditions in the presence of [Ir(cod)cod]₂ as catalyst. Further efforts are now devoted to the asymmetric version of this transformation.

1H NMR and 13C NMR spectra were recorded on 300 MHz Bruker AC 200 spectrometers. Chemical shifts are reported in ppm referenced to the residual proton resonances of the solvents. Mass spectra (MS) were obtained on GC-MS Hewlett-Packard HP 5971 spectrometers. Chemical shifts are reported in ppm referenced to tetramethylsilane (TMS).

**Methyl 3-(4-Bromophenylamino)-but-2-enoate (3q)**

Yield: 84%.

1H NMR (300.13 MHz, CDCl₃): δ = 2.00 (s, 3 H), 3.70 (s, 3 H), 4.74 (s, 1 H), 6.97 (d, J = 8 Hz, 2 H), 7.45 (d, J = 8 Hz, 2 H).

13C NMR (75.03 MHz, CDCl₃): δ = 20.7, 50.8, 87.0, 118.5, 126.2, 132.6, 138.8, 158.8, 171.1.

**Ethyl 3-(4-Bromophenylamino)-3-phenylacrylate (3s)**

Yield: 97%.

1H NMR (300.13 MHz, CDCl₃): δ = 1.98 (s, 3 H), 2.27 (s, 6 H), 3.71 (s, 3 H), 4.68 (s, 1 H), 6.83–7.12 (m, 4 H).

13C NMR (75.03 MHz, CDCl₃): δ = 15.4, 20.8, 20.9, 50.4, 87.0, 126.5, 130.5, 134.1, 137.3, 158.9, 170.5.

**Methyl 3-(4-Dimethylamino)but-2-enolate (3t)**

Yield: 82%.

1H NMR (300.13 MHz, CDCl₃): δ = 2.00 (s, 3 H), 2.46 (s, 3 H), 3.66 (s, 3 H), 3.79 (AB, J = 12 Hz, 2 H), 7.20–7.40 (m, 5 H).

13C NMR (75.03 MHz, CDCl₃): δ = 15.0, 59.9, 92.5, 116.1, 124.0, 128.6, 129.1, 130.1, 132.0, 136.0, 140.0, 158.9, 170.5.

**Ar-N,N-Dialkylaminoacrylates 3u–u; General Procedure**

In a Schlenk tube, methyl acetylacetate or tert-butyl acylacetate (1 equiv), and pyrrolidine (1.5 equiv) were successively added under argon. The neat reaction mixture was stirred at 25 °C. The reaction was monitored by TLC analysis. The crude mixture was recrystallized from a mixture of Et₂O–pentane.

**Methyl 3-(Pyrrolidino)but-2-enoate (3u)**

Yield: 88%.

1H NMR (300.13 MHz, CDCl₃): δ = 2.41 (s, 3 H), 3.25 (m, 4 H), 3.56 (s, 1 H), 4.11 (s, 1 H).

13C NMR (75.03 MHz, CDCl₃): δ = 16.6, 25.1, 47.9, 49.8, 82.7, 159.6, 169.5.

**tert-Butyl 3-(Pyrrolidino)but-2-enoate (3v)**

Yield: 89%.

1H NMR (300.13 MHz, CDCl₃): δ = 1.47 (s, 9 H), 1.91 (m, 4 H), 2.43 (s, 3 H), 3.28 (m, 4 H), 4.11 (s, 1 H).

13C NMR (75.03 MHz, CDCl₃): δ = 16.5, 25.2, 28.8, 47.8, 77.2, 85.1, 158.8, 169.2.

**β-Amino Esters 4a–u; General Procedure**

In a 25 mL stainless steel autoclave were placed under argon, the N-substituted β-amino acrylate (0.5 mmol, 1 equiv) and the iridium precatalyst (0.005 mmol, 1% mol). The mixture was degassed by three vacuum-filling with argon cycles before adding degassed and distilled CH₂Cl₂ (5 mL). Then, the autoclave was purged three times with H₂ and the vessel was pressurized to 10 or 20 bar. After 1–48 h (see text) at 50 °C, the autoclave was carefully opened, and the solvent was removed under reduced pressure. Conversion was determined by 1H NMR analysis of the crude mixture. Subsequently, the residue was purified by recrystallization from a mixture of Et₂O–pentane.

**Methyl 3-(Benzylationobutanoate (4a)**

Yield: 81.4%.

1H NMR (300.13 MHz, CDCl₃): δ = 1.15 (d, J = 6 Hz, 3 H), 2.44 (ABX, JAB = 15 Hz, JAX = 6 Hz, JBX = 6 Hz, 2 H), 3.16 (m, 1 H), 3.66 (s, 3 H), 3.79 (AB, JAB = 12 Hz, 2 H), 7.20–7.34 (m, 5 H).

13C NMR (75.03 MHz, CDCl₃): δ = 20.5, 41.4, 49.7, 51.2, 51.5, 126.9, 128.1, 128.4, 140.4, 172.8.
Ethyl 3-(Benzylamino)butanoate (4b)

1H NMR (300.13 MHz, CDCl3): δ = 1.15 (d, J = 6 Hz, 3 H), 1.24 (t, J = 7.5 Hz, 3 H), 2.42 (ABX, JAB = 15 Hz, JAX = 6 Hz, JBX = 6 Hz, 2 H), 3.16 (m, 1 H), 3.79 (AB, JAB = 12 Hz, 2 H), 4.12 (q, J = 7 Hz, 2 H), 7.20–7.35 (m, 5 H).

13C NMR (75.03 MHz, CDCl3): δ = 14.2, 20.5, 41.7, 49.7, 51.2, 60.3, 126.9, 128.1, 128.4, 140.4, 172.3.

HRMS: m/z calec for C10H16NO2 [M + CH3]+: 192.1024; found: 192.1013.

tert-Butyl 3-(Benzylamino)butanoate (4c)

1H NMR (300.13 MHz, CDCl3): δ = 1.15 (d, J = 6 Hz, 3 H), 1.44 (s, 9 H), 2.34 (ABX, JAB = 15 Hz, JAX = 9 Hz, JBX = 6 Hz, 2 H), 3.12 (m, 1 H), 3.78 (AB, JAB = 13.5 Hz, 2 H), 7.20–7.35 (m, 5 H).

13C NMR (75.03 MHz, CDCl3): δ = 20.4, 28.1, 42.9, 49.9, 51.2, 80.4, 126.9, 128.1, 128.4, 140.5, 171.7.

HRMS: m/z calec for C10H16NO2 [M + CH3]+: 206.1181; found: 206.1196.

Methyl 3-(Isopropylamino)butanoate (4e)

1H NMR (300.13 MHz, CDCl3): δ = 1.03 (dd, J = 3, 9 Hz, 6 H), 1.09 (d, J = 6 Hz, 3 H), 1.25 (t, J = 6 Hz, 3 H), 2.36 (ABX, JAB = 15 Hz, JAX = 6 Hz, JBX = 6 Hz, 2 H), 2.89 (m, 1 H), 3.18 (m, 1 H), 4.12 (q, J = 7 Hz, 2 H).

13C NMR (75.03 MHz, CDCl3): δ = 14.2, 21.0, 23.0, 23.5, 41.9, 45.3, 47.2, 60.2, 172.4.

HRMS: m/z calec for C8H19NO2: 159.1259; found: 159.1271.

Ethyl 3-(Isopropylamino)butanoate (4e)

1H NMR (300.13 MHz, CDCl3): δ = 1.03 (dd, J = 3, 9 Hz, 6 H), 1.09 (d, J = 6 Hz, 3 H), 1.25 (t, J = 6 Hz, 3 H), 2.36 (ABX, JAB = 15 Hz, JAX = 6 Hz, JBX = 6 Hz, 2 H), 2.89 (m, 1 H), 3.18 (m, 1 H), 4.12 (q, J = 7 Hz, 2 H).

13C NMR (75.03 MHz, CDCl3): δ = 14.2, 21.0, 23.0, 23.5, 41.9, 45.3, 47.2, 80.3, 171.8.

HRMS: m/z calec for C8H19NO2 [M – CH3]+: 158.1181; found: 158.1197.

tert-Butyl 3-(Isopropylamino)butanoate (4f)

1H NMR (300.13 MHz, CDCl3): δ = 1.03 (dd, J = 3, 9 Hz, 6 H), 1.08 (d, J = 6 Hz, 3 H), 1.44 (s, 9 H), 2.27 (ABX, JAB = 15 Hz, JAX = 9 Hz, JBX = 6 Hz, 2 H), 2.89 (m, 1 H), 3.13 (m, 1 H).

13C NMR (75.03 MHz, CDCl3): δ = 20.9, 23.0, 23.6, 28.1, 43.1, 45.2, 47.3, 80.3, 171.8.


Methyl 3-(Bromophenylamino)butanoate (4n)

1H NMR (300.13 MHz, CDCl3): δ = 1.27 (d, J = 6 Hz, 3 H), 2.53 (ABX, JAB = 15 Hz, JAX = 6 Hz, JBX = 6 Hz, 2 H), 3.69 (s, 3 H), 3.88 (m, 1 H), 6.50 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H).

13C NMR (75.03 MHz, CDCl3): δ = 20.5, 40.8, 46.1, 51.7, 110.5, 117.1, 122.4, 127.2, 130.4, 144.8, 172.3.

HRMS: m/z calec for C11H15BrNO2: 271.0208; found: 271.0223.

Methyl 3-(3′,4′-Dimethoxyphenylamino)butanoate (4o)

1H NMR (300.13 MHz, CDCl3): δ = 1.32 (d, J = 6 Hz, 3 H), 2.22 (s, 3 H), 2.26 (s, 3 H), 2.58 (ABX, JAB = 15 Hz, JAX = 3 Hz, JBX = 6 Hz, 2 H), 2.74 (s, 3 H), 3.59 (m, 1 H), 6.45–6.53 (m, 2 H), 6.71 (d, J = 9 Hz, 1 H).

Synthesis 2009, No. 15, 2627–2633 © Thieme Stuttgart · New York
References


(20) It was reported that trifluoroethanol was the best solvent for the hydrogenation of enamino esters and β-N-arylenamino esters in the presence of rhodium catalysts; see references 15 and 16.