



A Simple and Fast Synthetic Pathway of β -Enamino-Esters by Condensation of β -Keto Ester with Aliphatic and Aromatic Amines in Ethanol

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The β -keto ester undergoes condensation reactions with aliphatic and aromatic amines in ethanol to give high-yielding β -enamino ester. The method is simple, cost-effective and environmentally benign. Structural characterization of the synthesized compounds was carried out by spectroscopic methods (¹H NMR, ¹³C NMR and DEPT).

Keywords: β -Keto esters, β -Enamino esters.

INTRODUCTION

The β -enamino esters are useful synthones for the synthesis of various pharmaceuticals¹ and bioactive heterocycles^{2,3} such as 1,4-dihydropyridines⁴ pyrazoles, oxazoles, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetrone acids and tetrahydro phenanthridines⁵. They have been utilized for the preparation of different important antibacterial, anti-inflammatory, anticonvulsant and antitumour agents⁶. Moreover, they are useful intermediates for the preparation of α,β -aminoacids⁷, azocompounds⁸ and alkaloids⁹. Given their importance in the field of chemical synthesis, research continues to grow to develop a variety of more effective methods in terms of reduction of time, yield and selectivity.

Different synthetic ways are used, we can cite as examples:

(1) The condensation of β -keto esters with amines in the presence of catalysts, such as: NaAu-ClO₄·2H₂O¹⁰; Bi(TFA)₃¹¹; Zn(ClO₄)₂·6H₂O¹²; CeCl₃·7H₂O¹³; SiO₂/HClO₄¹⁴; (AlPO₄)¹⁵; (2) Addition of amines to alkylpropiolates or dialkylacetylendicarboxylates a solvent-free¹⁶; (3) Hydroamidation of electron-deficient terminal alkynes by amides in the presence of a Pd-catalyst¹⁷; (4) Addition of anilines to alkyl-propiolates in the presence of catalyzed by Au(I)¹⁸; AgNTf₂¹⁹; (5) Treatment of aliphatic or aromatic nitriles with an excess of α -bromo esters in the presence of activated zinc dust²⁰; (6) Reaction of aryl nitriles with potassium ethyl malonate in the presence of zinc chloride²¹; (**Scheme-I**).

However, these methods suffer from one or more drawbacks such as the use of expensive or less readily available reagents, vigorous reaction conditions, longer reaction times, unsatisfactory yields, low selectivity or the use of toxic solvents that limit these methods to small scale synthesis.

Due to the importance of these compounds in organic synthesis, the development of facile and efficient synthetic methods to the β -enamino esters is of prime necessity. It involves the condensation of amines on β -keto esters (**Scheme-II**).

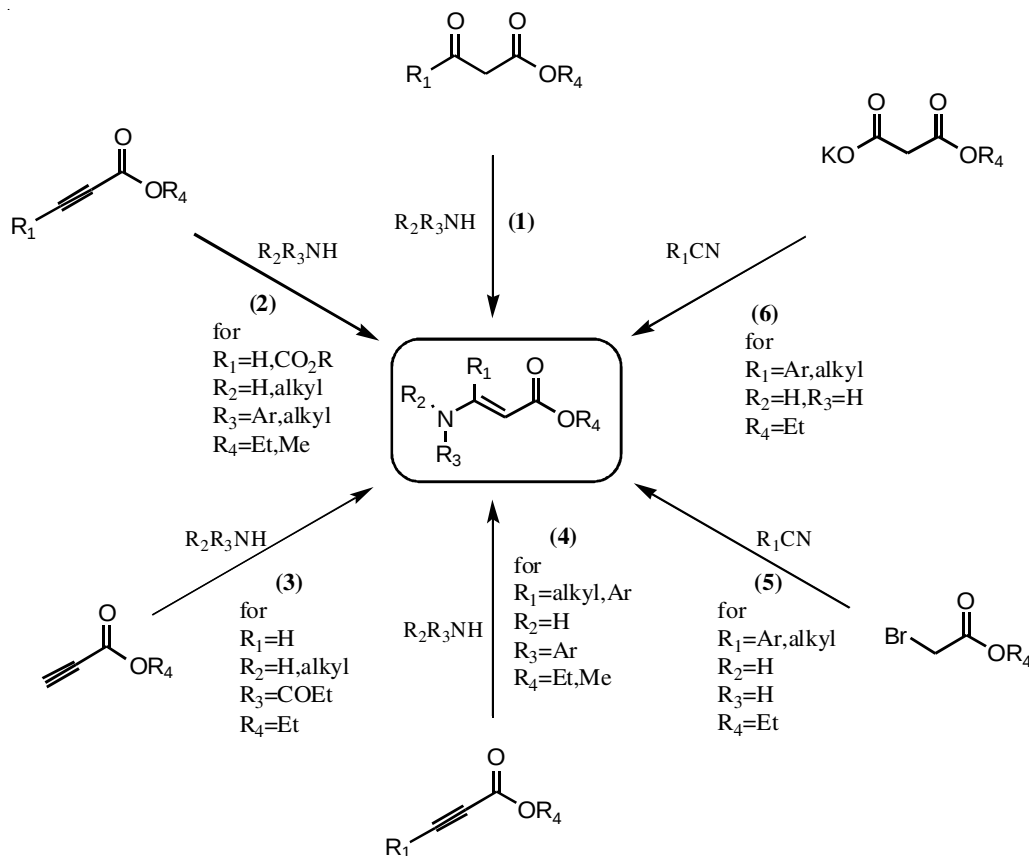
EXPERIMENTAL

¹H, ¹³C, DEPT spectra were recorded on a Bruker Avance 300. Chemical shifts are given in parts per million (ppm) with respect to internal TMS for all recorded NMR spectra and J values are quoted in hertz (Hz). The nuclear magnetic resonances were recorded on a Bruker AC-300 device.

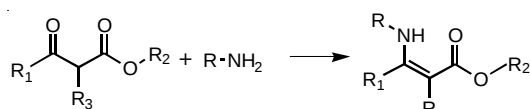
General procedure

Operating mode of β -keto esters with aliphatic primary amines: In a three-necked 100 mL flask equipped with a magnetic stirrer with heating and cooling, the β -keto ester (1 eq) was placed in 10 mL of ethanol and then we add an equivalent of primary amine in 10 mL of EtOH. The mixture is subjected to stirring and heated under reflux. The reaction was followed by thin layer chromatography TLC. The solvent was evaporated under reduced pressure.

Ethyl 2-(allylamino)cyclohex-1-ene carboxylate (1): Yield: 82 %; ¹H NMR (CDCl₃) δ ppm: 1.20 (t, J = 7 Hz, 3H,



Scheme-I: Synthesis of b-enamino esters

Scheme-II: Synthesis of β -enamino esters

CH₃); 1.46-1.64 (m, 4H); 2.20-2.30 (q, $J = 5.85$ Hz, 4H); 3.76 (t, 2H, -CH₂-); 4.08 (q, $J = 7$ Hz, 2H, -CH₂-); 5.1 (dd, $J = 10.5$ Hz, $J = 1.3$ Hz, 1H, =CH); 5.2 (dd, $J = 17$ Hz, $J = 1.3$ Hz, 1H, =CH); 5.7 (ddt, $J = 15.3$ Hz, $J = 10.2$ Hz, $J = 5.1$ Hz, 1H, =CH); 9.01 (s, 1H, NH); ¹³C NMR (CDCl₃) δ ppm: 14.65 (CH₃); 22.25 (CH₂); 22.69 (-CH₂-); 23.82 (-CH₂-); 26.01 (-CH₂-); 44.44 (-CH₂-); 58.64 (-CH₂-); 90.14 (=C); 115.54 (=CH); 135.49 (=C); 159.40 (=CH); 170.88 (C=O).

Ethyl 2-(2,2-dimethoxyethylamino)-cyclohex-1-ene carboxylate (2): Yield: 87 %; ¹H NMR (CDCl₃) δ ppm: 1.20 (t, $J = 7$ Hz, 3H, CH₃); 1.43-1.64 (m, 4H); 2.14-2.29 (q, $J = 5.85$ Hz, 4H); 3.24 (t, 2H, -CH₂-); 3.34 (s, 6H, CH₃); 4.08 (q, $J = 7$ Hz, 2H, -CH₂-); 4.35 (t, $J = 5$ Hz, 1H, -CH-); 8.90 (s, 1H, NH); ¹³C NMR (CDCl₃) δ ppm: 14.60 (CH₃); 22.28 (-CH₂-); 22.63 (-CH₂-); 23.85 (-CH₂-); 26.58 (-CH₂-); 44.03 (-CH₂-); 54.13 (CH₃); 58.65 (-CH₂-); 90.66 (=C); 103.53 (-CH); 158.66 (=C); 170.73 (C=O).

Méthyl 2-(2,2-dimethoxyethylamino)cyclopent-1-ene carboxylate (3): Yield: 84 %; ¹H NMR (CDCl₃) δ ppm: 1.47-1.87 (m, 2H); 2.43-2.60 (m, 4H); 3.27 (t, $J = 5.5$ Hz, 2H, -CH₂-); 3.65 (s, 6H, CH₃); 4.35 (t, $J = 5$ Hz, 1H, -CH-); 7.42 (s, 1H, NH); ¹³C NMR (CDCl₃) δ ppm: 20.85 (CH₂-); 29.13 (-CH₂-); 32.20 (-CH₂-); 46.75 (-CH₂-); 50.14 (CH₃); 54.49 (CH₃); 94.15 (=C); 103.76 (CH); 155.33 (C=O); 168.60 (=C).

(Z)-methyl 3-(allylamino)but-2-enoate (4): Yield: 80 %;

¹H (CDCl₃) δ ppm: 1.83 (s, 3H, CH₃); 3.54 (s, 3H, CH₃); 3.75 (t, 2H, -CH₂-); 4.41 (s, 1H, =CH); 5 (dd, $J = 10.4$ Hz, $J = 1.1$ Hz, 1H, =CH); 5.1 (dd, $J = 17.2$ Hz, $J = 1.1$ Hz, 1H, =CH); 5.8 (ddt, $J = 15.2$ Hz, $J = 10.1$ Hz, $J = 5$ Hz, 1H, =CH); 8.57 (s, 1H, NH); ¹³C NMR (CDCl₃) δ ppm: 29.69 (CH₃); 45.15 (-CH₂-); 49.69 (CH₃); 82.39 (=CH); 115.91 (=CH); 134.73 (=CH); 162.02 (Cq); 170.88 (C=O).

(Z)-Méthyl 3-(2,2-dimethoxyethylamino)but-2-enoate (5): Yield: 75 %; ¹H NMR (CDCl₃) δ ppm: 2.45 (s, 3H, CH₃); 3.81-3.89 (m, 7H); 4.02 (s, 3H, CH₃); 4.91-4.98 (m, 2H); 8.57 (s, 1H, NH); NMR DEPT (CDCl₃) δ ppm: 29.08 (CH₃); 45.10 (-CH₂-); 50.25 (CH₃); 82.44 (=CH); 103.73 (-CH).

(Z)-Diméthyl 3-(2,2-dimethoxyethylamino)pent-2-enedioate (6): Yield: 74 %; ¹H NMR (CDCl₃) δ ppm: 3.16-3.30 (m, 4H); 3.32 (s, 6H, CH₃); 3.53 (s, 3H, CH₃); 3.63 (s, 3H, CH₃); 4.30 (t, $J = 5.5$ Hz, 1H, -CH); 4.44 (s, 1H, =CH); 8.51 (s, 1H, NH); NMR DEPT (CDCl₃) δ ppm: 38.94 (-CH₂-); 45.95 (-CH₂-); 50.52 (CH₃); 52.78 (CH₃); 54.90 (2CH₃); 85.36 (=CH); 103.80 (-CH).

Condensation with aniline: In a test tube is placed the phenyl with β -keto cyclic. The obtained product was washed with ethyl ether.

Ethyl 2-(phenylamino)cyclohex-1-ene carboxylate (7): Yield: 85 %; ¹H NMR (CDCl₃) δ ppm: 1.25 (t, $J = 7$ Hz, 3H, CH₃); 1.69 (d, $J = 6.61$, 4H); 2.27-2.44 (dt, $J = 5.86$ Hz, 22.66 Hz, 4H); 4.14 (q, $J = 7$ Hz, 2H, -CH₂-); 7.10-7.20 (m, 3H, H_{arom}); 7.30-7.40 (m, 2H, H_{arom}); 10.81 (s, 1H, NH); ¹³C NMR (CDCl₃) δ ppm: 14.62 (CH₃); 21.93 (-CH₂-); 22.24 (-CH₂-); 23.75

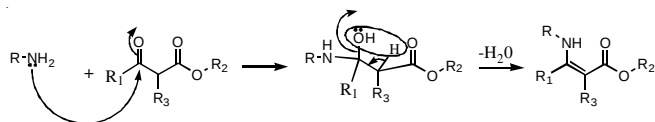
(-CH₂-); 27,65 (-CH₂-); 58,90 (-CH₂-); 92,43 (C); 124,20 (C_{arom}); 129,22 (C_{arom}) 139,37(C); 156,51 (C_{arom}); 170,00 (C=O).

Methyl 2-(2-aminophenylamino) cyclopent-1-ene carboxylate (8): Yield: 83 %; ¹H NMR (CDCl₃) δ ppm: 1.76-1.91 (m, 2H); 2.44-2.66 (dt, 4H); 3.76 (s, 3H, CH₃); 6.68-6.81 (m, 2H, H_{arom}); 6.97-6.10 (m, 2H, H_{arom}); 8.71 (s, 1H, NH).

RESULTS AND DISCUSSION

The results of the condensation of these β -keto esters with amines are recorded on Table-1. As has already been discussed, β -enamino esters are obtained *via* condensation reactions of β -keto esters with primary amines in ethanol under reflux, or at room temperature under solvent free conditions. The reaction yields vary from 70 to 87 %.

The method averred to be very selective, since the ketonic carbonyl group is more electrophilic than ester, (Alternatively, the ketone loses no resonance when it accepts a nucleophile, while ester loses the minor contributor of resonance), according to the following mechanism:



Spectroscopic (¹H NMR, ¹³C NMR) characteristics data, confirming the presence of β -enamino esters: The ¹H NMR spectra analysis of the compounds obtained in Table-1, shows that the compounds **2**, **3**, **5** and **6** exhibit, characteristic signals: a high field singlet signal between 3.43 and 3.45 ppm corresponding to 2(OCH₃) and a second signal in the form of a triplet in the range 4.30-4.35 ppm corresponding to proton CH (OMe)₂ of acetyl, while a massive characterizing proton CH₂CH(OMe)₂ resonates in the range 3.24-3.27 ppm.

The ¹H NMR spectra of compounds **1** and **4** exhibit a doublet split triplet signal in the range 5.60-5.90 ppm corresponding to the proton HC=CH₂, the chemical shifts of the protons of the double bond H_{cis} and H_{trans} appear almost superimposed in the form of a split doublet in the range 5-5.40 ppm, followed by an apparent signal in the range 3.7-3.8 ppm corresponding to the protons of CH₂-CH=CH₂.

We also noted that a singlet signal is observed in the range 4.41-4.44 ppm for compounds **4**, **5** and **6** corresponding to the ethylene protons.

In case of ¹³C NMR it is suggested that on the one hand, the disappearance of the function C=O of the ketone β -keto esters and on the other hand the appearance of two ethylenic carbons in α and β of the ester function.

In conclusion, we have prepared eight enaminos derived from β -keto esters, in simple terms and with very good yields.

TABLE-1
RESULTS OF THE CONDENSATION OF THESE β -KETO ESTERS WITH AMINES

Entry	β -keto ester	Amine	Operating conditions	Resulting products	Yield (%)
01			Ethanol, 5h under reflux		82
02			Ethanol, 4h under reflux		87
03			Ethanol, 3h under reflux		84
04			Ethanol, 5h under reflux		80
05			Ethanol, 4h under reflux		75
06			Ethanol, 6h under reflux		74
07			Ethanol, 6h under reflux		85
08			Ethanol, 6h under reflux		83

The products thus obtained were characterized by various spectroscopic methods.

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