Efficient Synthetic Method for β-Enamino Esters Using Ultrasound

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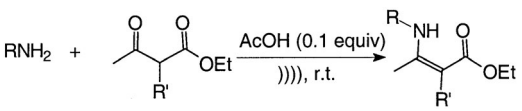
Abstract: β-Keto esters react with a variety of amines in the presence of 0.1 equivalents of acetic acid without any solvents under ultrasound to give good yields of the corresponding β-enamino esters.

Keywords: ultrasound, β-enamino esters, β-keto esters, amines

β-Enaminones are very attractive molecules available from the corresponding β-dicarbonyl compounds.[1–13] They are basic and versatile structures for the synthesis of natural therapeutic and synthetic biologically active analogues including taxol,[2,4,14–19] anticonvulsivant,[3,14] anti-inflammatory,[14,20] and antitumor agents,[14,21] as well as quinolone antibacterials[14,22,23] and quinoline antimalarials. β-Enaminones also possess good stability under simulated physiological pH conditions and low toxicity.[3,8] A number of reviews have been published about the chemistry of enamines,[24,25] their hydrolysis under a variety of conditions, their physicochemical properties and uses.[26–31] Among the methods for generating β-enaminones, condensation of amines and β-dicarbonyl compounds is a classical method in which the azeotropic removal of water is affected by refluxing in aromatic solvent.[2,5,6,10,13,32–36] A variety of other methods utilizing Al_2O_3,[4] SiO_2,[37] montmorillonite K10,[38,39] and $NaAuCl_4$[40] as catalysts have been reported. However, in spite of their potential utility, some of these methods suffer from drawbacks including the use of non-available and costly reagents, longer reaction times, higher temperatures, lower yields, use of hazardous solvents (toluene or benzene), side products (amides) and cumbersome product isolation procedures.

In order to circumvent the problems mentioned above as well as developing an environmentally friendly procedure, we describe herein a very fast and mild procedure for the synthesis of β-enamino esters from amines and β-keto esters. This procedure utilizes ultrasound irradiation in the presence of acetic acid (Scheme 1) and the results are summarized in Table 1.



Scheme 1

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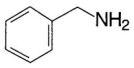
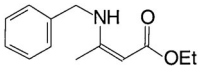
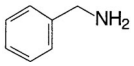
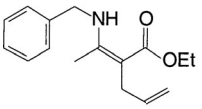
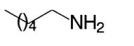
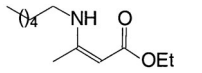
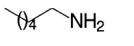
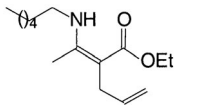
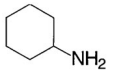
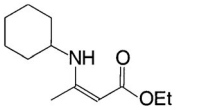
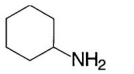
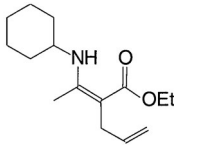
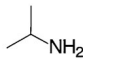
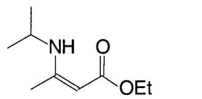
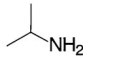
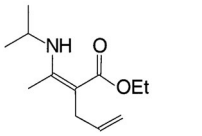
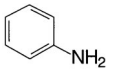
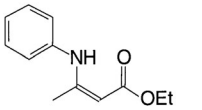
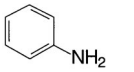
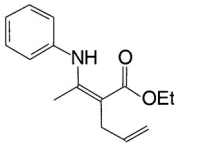
The usual preparation of enamines involves the nucleophilic addition of amines to carbonyl compounds. The importance of nucleophilicity of the nitrogen to form

Table 1 Synthesis of β-Enamino Esters from Amines and β-Keto Esters under Sonication

Entry	Amine	Product	Time (h)	Isolated Yields (%)
1			0.2	98
2			0.5	98[a]
3			0.2	96
4			0.5	92[a]
5			0.2	96
6			2.0	94[a]
7			0.2	90
8			3.0	89[a]
9			2.0	86
10			3.0	60[a]

[a] Two equivalents of amine were used.

enamines has been documented and it can be determined by stereoeletronic effects of amines.[41–44] As shown in Table 1, the reactions where more nucleophilic amines were used (i.e. benzylamine, cyclohexylamine, and hexylamine) gave the products in almost quantitative yields in a short period of time. However, when very weak amines like aniline were used, the reaction proceeded more slowly but was more effective than other methods in terms of yields and reaction time. For instance, entry 9 (aniline and ethyl acetoacetate) gave the enamine in 86% instead of 50–65% yield (previously reported methods).[39,45] The *Z* geometry in these compounds is secured by intramolecular hydrogen bonding (in ^{1}H NMR, the NH hydrogen atom is typically shifted downfield, from 10.5 to 8.5 ppm). Additionally, there are distinct advantages of this methodology since it provides regioselective products. Longer reaction times by heating methodology resulted in greater amounts of amides, since the enamines are converted into the amides with one equivalent of water at high temperature,[1] providing in this case lower selectivity.

In conclusion, we propose a novel and efficient approach for rapid synthesis of the β-enamino esters using acetic acid as an inexpensive and environmentally benign catalytic system. Advantages of this method are mild reaction conditions, economical procedure, improved yields and enhanced reaction rates, simple experimental and separation procedures.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer in $CDCl_3$/Me_4Si. Capillary CG analyses were performed on a HP 6890 series chromatograph equipped with a split/splitless injector and FID detector. An ultrasound bath (water), Thornton, 50/60 Hz, 110/220 V, was used.

Preparation of β-Enamino Esters; Typical Procedure

A mixture of ethyl acetoacetate or ethyl 2-acetylpent-4-enoate (2 mmol), amine (2 mmol) and acetic acid (0.2 mmol) was placed in an ultrasound bath USC 700, 40 KHz, 100 W (the temperature of the bath never exceeding 30 °C) for the time (by capillary GC analysis) reported in Table 1. At the end of the reaction, EtOH (5 mL) was added, the solution was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was distilled after the removal of unreacted starting material by Kugelrohr apparatus at reduced pressure to give the pure product as a yellow oil.

Ethyl (2*Z*)-3-(Benzylamino)but-2-enoate[45] (Entry 1)

Yellow oil, bp 110–115 °C/0.20 Torr.

IR (film): 1655, 1605 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3 H, *J* = 7.1 Hz), 1.90 (s, 3 H), 4.10 (q, 2 H, *J* = 7.1 Hz), 4.42 (d, 2 H, *J* = 6.4 Hz), 4.55 (s, 1 H), 7.22–7.40 (m, 5 H), 8.95 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 19.5, 24.1, 46.8, 58.5, 83.2, 126.8, 127.4, 128.8, 138.8, 162.0, 170.6.

Ethyl (2*Z*)-3-(Hexylamino)but-2-enoate[45] (Entry 3)

Yellow oil, bp 105–110 °C/0.20 Torr.

IR (film): 1655, 1606 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 6.7 Hz), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.22–1.41 (m, 6 H), 1.51–1.60 (m, 2 H), 1.91 (s, 3 H), 3.19 (q, 2 H, *J* = 6.7 Hz), 4.08 (q, 2 H, *J* = 7.1 Hz), 4.42 (s, 1 H), 8.56 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 14.3, 18.9, 22.2, 26.2, 30.1, 31.2, 42.7, 57.8, 81.5, 161.5, 170.3.

Ethyl (2*Z*)-3-(Cyclohexylamino)but-2-enoate[45] (Entry 5)

Yellow oil, bp 110–115 °C/0.35 Torr.

IR (film): 1654, 1607 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, 3 H, *J* = 7.1 Hz), 1.26–1.89 (m, 10 H), 1.93 (s, 3 H), 3.29–3.34 (m, 1 H), 4.08 (q, 2 H, *J* = 7.1 Hz), 4.39 (s, 1 H), 8.64 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 19.1, 24.6, 25.4, 34.5, 51.4, 58.1, 60.4, 81.8, 160.8, 170.5.

Ethyl (2*Z*)-3-(Isopropylamino)but-2-enoate[45] (Entry 7)

Yellow oil, bp 75 °C/2.00 Torr.

IR (film): 1656, 1608 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, 6 H, *J* = 6.4 Hz), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.92 (s, 3 H), 3.63–3.74 (m, 1 H), 4.08 (q, 2 H, *J* = 7.1 Hz), 4.42 (s, 1 H), 8.48 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.1, 24.0, 44.3, 58.0, 81.6, 160.7, 170.5.

Ethyl (2*Z*)-3-Anilinobut-2-enoate[45] (Entry 9)

Yellow oil, bp 125–130 °C/0.20 Torr.

IR (film): 1648, 1589 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, 3 H, *J* = 7.1 Hz), 1.99 (s, 3 H), 4.17 (q, 2 H, *J* = 7.1 Hz), 4.69 (s, 1 H), 7.08 (d, 2 H, *J* = 7.5 Hz), 7.15 (t, 1 H, *J* = 7.5 Hz), 7.32 (t, 2 H, *J* = 7.5 Hz), 10.38 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 20.5, 58.9, 86.2, 124.6, 125.1, 129.2, 139.5, 159.1, 170.6.

Ethyl (2*Z*)-2-[1-(Benzylamino)ethylidene]pent-4-enoate[2] (Entry 2)

Yellow oil, bp 125–130 °C/0.15 Torr.

IR (film): 1645, 1598 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3 H, *J* = 7.0 Hz), 1.91 (s, 3 H), 3.01 (d, 2 H, *J* = 5.4 Hz), 4.12 (q, 2 H, *J* = 7.0 Hz), 4.43 (d, 2 H, *J* = 5.9 Hz), 4.89–4.97 (m, 2 H), 5.76–5.88 (m, 1 H), 7.26–7.32 (m, 5 H), 9.77 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 14.7, 31.2, 46.9, 58.6, 90.3, 112.9, 126.7, 127.0, 128.6, 138.3, 139.1, 162.5, 170.6.

Ethyl (2*Z*)-2-[1-(Hexylamino)ethylidene]pent-4-enoate[2] (Entry 4)

Yellow oil, bp 120–125 °C/0.15 Torr.

IR (film): 1645, 1598 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 6.7 Hz), 1.24 (t, 3 H, *J* = 7.0 Hz), 1.22–1.41 (m, 6 H), 1.52–1.61 (m, 2 H), 1.94 (s, 3 H), 2.99 (d, 2 H, *J* = 5.7 Hz), 3.18 (t, 2 H, *J* = 7.0 Hz), 4.11 (q, 2 H, *J* = 7.0 Hz), 4.91–4.97 (m, 2 H), 5.75–5.88 (m, 1 H), 9.36 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 13.9, 21.9, 25.9, 29.7, 30.6, 30.9, 42.6, 58.3, 88.2, 111.8, 137.9, 159.9, 169.8.

Ethyl (2*Z*)-2-[1-(Cyclohexylamino)ethylidene]pent-4-enoate[2] (Entry 6)

Yellow oil, bp 105–110 °C/0.35 Torr.

IR (film): 1644, 1597 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.94 (m, 10 H), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.96 (s, 3 H), 2.98 (d, *J* = 5.8 Hz, 2 H), 3.30–3.34 (m, 1 H), 4.10 (q, 2 H, *J* = 7.1 Hz), 4.87–4.96 (m, 2 H), 5.76–5.88 (m, 1 H), 9.46 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.4, 22.3, 26.4, 30.2, 31.1, 31.3, 43.2, 58.3, 88.7, 112.5, 138.4, 160.5, 170.5.

Ethyl (2*Z*)-2-[1-(Isopropylamino)ethylidene]pent-4-enoate[2] (Entry 8)
Yellow oil, bp 75–80 °C/1.00 Torr.

IR (film): 1646, 1596 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, 6 H, *J* = 6.4 Hz), 1.25 (t, 3 H, *J* = 7.1 Hz), 1.97 (s, 3 H), 2.99 (d, 2 H, *J* = 6.4 Hz), 3.62–3.76 (m, 1 H), 4.10 (q, 2 H, *J* = 7.1 Hz), 4.88–4.97 (m, 2 H), 5.77–5.86 (m, 1 H), 9.38 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 24.1, 31.2, 44.4, 58.4, 88.8, 112.6, 138.5, 159.7, 170.6.

Ethyl (2*Z*)-2-(1-Anilinoethylidene)pent-4-enoate[2] (Entry 10)
Yellow oil, bp 125–130 °C/0.10 Torr.

IR (film): 1642, 1598 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, *J* = 7.2 Hz), 2.01 (s, 3 H), 3.06 (d, 2 H, *J* = 5.8 Hz), 4.19 (q, 2 H, *J* = 7.2 Hz), 4.93–5.13 (m, 2 H), 5.69–5.90 (m, 1 H), 7.02 (d, 2 H, *J* = 7.5 Hz), 7.17 (t, 1 H, *J* = 7.5 Hz), 7.30 (t, 2 H, *J* = 7.5 Hz), 11.06 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 16.4, 31.4, 58.1, 93.8, 113.3, 124.4, 124.6, 128.9, 137.5, 139.9, 157.9, 170.5.

Acknowledgment

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