

An Easy Synthesis of Enaminones in Water as Solvent

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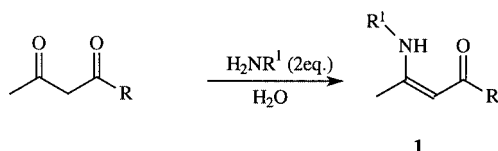
Abstract: Enaminones were prepared from β -ketoesters or 1,3-diketones and primary amines in water as solvent

Key words: β -ketoesters, 1,3-diketones, β -enaminones

Enaminones and related compounds possessing the structural unit $N-C=C-Z$ ($Z = COR, CO_2R, CN$, etc.) are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.¹

Some procedures reported for the synthesis of β -enaminocarbonyl derivatives include the reaction of amines and 1,3-diketones supported over clay K_{10} /ultra-sound² or silica under microwave irradiation,³ reaction of β -amino ketones in the presence of triethylamine promoted by $Pd(II)$,⁴ and reactions of α -metalated imines with esters.⁵ However, the generally employed method for the preparation entails the reaction between ammonia or a primary or secondary amine with 1,3-dicarbonyl compound in benzene solution with azeotropic removal of the water formed.^{6–10}

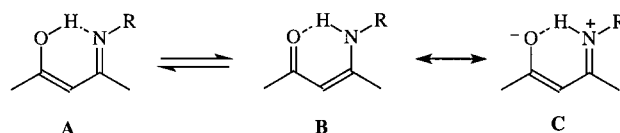
We report here, a simple procedure for the synthesis of β -enamino esters and enaminoketones (**1**) starting from β -ketoesters or 1,3-diketones and primary amines in water as solvent (Scheme 1). The main advantages of this methodology are: (a) the reaction is simple to perform; (b) the reaction occurs at room temperature; (c) the yields are good to high, (d) acid catalysis is not necessary, (e) the reaction works for a variety of primary amines; and (f) purification of the enaminones is not necessary. With secondary amines or simple carbonyl compounds, no reaction was observed. The reaction worked very well to soluble amines, but with less soluble amines the yield was moderated and it was necessary to use high excess of amine (3 equivalents). When β -ketoester and 1,3-diketones reacted with ethylene-diamine, diamines were observed as products (**1h** and **1m**).



Scheme 1

Since there are two carbonyl groups in the starting material and 2 equivalents of amine were added, there should be several products in this reaction, i.e., the amine may react with one or both of carbonyl groups. Thus, there should be three products from β -ketoester and two from 1,3-diketone, however, only enaminones were observed as products. This probably occurs because the acetyl portion of the starting dicarbonyl compounds is more reactive than the ester or aromatic conjugated carbonyl. When the enaminone is formed, it is stabilized by resonance, blocking the formation of other products. The conjugation effect also justifies the formation of only one product from acetylacetone.

The probable explanation for the formation of enaminones in water is their tautomeric forms (**A** and **B**) associated with the hydrogen bond.^{11,12} Enaminones of all types exist predominantly in the carbonyl form and are stabilized by the contribution of the zwitterionic form (**C**),¹³ which can be solvated by water preventing hydrolysis of the formed enaminone. This explanation can be supported by the fact that no reaction was observed using secondary amines or simple carbonyl compounds (Scheme 2).



Scheme 2

In summary, we have provided a remarkably viable alternative route for the synthesis of enaminones using water as solvent. We have found, at present, only one limitation: the low solubility of some primary amines in water prevents the preparation of enaminones in good yields. The characterization of the enaminones is very known, therefore, only the basic identification (NMR and IR) was done.

Enaminones 1; General Procedure

The β -ketoester or 1,3-diketones (1 mmol) was added, at r.t., to amino compound (2 mmol) in H_2O (5 mL) and stirred for the time indicated (Table). When the enaminone formation was completed (monitored by GC), the reaction mixture was washed with brine to remove excess amine and then extracted with CH_2Cl_2 .

Table Enaminones **1a-o**

Entry	R	R ¹	Reaction Time (h)	Yield (%) ^b	IR ν (cm ⁻¹) ^c	¹ H NMR (300 MHz, CDCl ₃) δ (ppm), <i>J</i> (Hz) ^d	¹³ C NMR (75 MHz, CDCl ₃) δ (ppm) ^d
1a	-OCH ₂ CH ₃	-CH ₂ CH ₃	6	75	1651, 1605	1.21 (t, 3 H, <i>J</i> = 7), 1.24 (t, 3 H, <i>J</i> = 7), 1.92 (s, 3 H), 3.25 (quin, 2 H, <i>J</i> = 7), 4.07 (q, 2 H, <i>J</i> = 7), 4.42 (s, 1 H), 8.48 (br s, 1 H)	14.86, 15.82, 19.40, 37.84, 58.36, 81.54, 162.01, 170.83
1b	-OCH ₂ CH ₃	-CH(CH ₃) ₂	10	65	1654, 1609	1.21 (d, 6 H, <i>J</i> = 6.5) 1.24 (t, 3 H, <i>J</i> = 7), 1.94 (s, 3 H), 3.68 (m, 1 H), 4.08 (q, 2 H, <i>J</i> = 7), 4.39 (s, 1 H), 8.49 (br s, 1 H)	14.76, 19.28, 24.20, 44.53, 58.26, 81.82, 160.93, 170.70
1c	-OCH ₂ CH ₃	CH ₂ CH=CH ₂	7	88	1648, 1606	1.24 (t, 3 H, <i>J</i> = 7.1), 1.90 (s, 3 H), 3.83 (m, 2 H), 4.07 (q, 2 H, <i>J</i> = 7.1), 4.48 (s, 1 H), 5.15 (d, 1 H, <i>J</i> = 10.4), 5.21 (d, 1 H, <i>J</i> = 17.2), 5.80–5.92 (m, 1 H), 8.67 (br s, 1 H)	14.66, 19.03, 45.16, 58.30, 82.85, 115.79, 134.92, 161.89, 170.57
1d	-OCH ₂ CH ₃	-CH ₂ CH ₂ OH	4	80	1629, 1588	1.23 (t, 3 H, <i>J</i> = 7.1), 1.94 (s, 3 H), 3.36 (q, 2 H, <i>J</i> = 5.5), 3.71 (t, 2 H, <i>J</i> = 5.5), 3.84 (br s, 1 H) 4.05 (q, 2 H, <i>J</i> = 7.1), 4.46 (s, 1 H), 8.62 (br s, 1 H)	14.65, 19.64, 45.22, 58.51, 61.79, 82.58, 162.32, 170.86
1e	-OCH ₂ CH ₃	- <i>c</i> -C ₆ H ₁₁	11	86	1655, 1608	1.24 (t, 3 H, <i>J</i> = 7.1), 1.26–1.88 (m, 10 H), 1.93 (s, 3 H), 3.29–3.33 (m, 1 H), 4.07 (q, 2 H, <i>J</i> = 7.1), 4.38 (s, 1 H), 8.64 (br s, 1 H)	14.73, 19.21, 24.71, 25.47, 34.56, 51.41, 58.23, 60.36, 81.78, 160.79, 170.62
1f	-OCH ₂ CH ₃	-CH ₂ C ₆ H ₅	12	73	1658, 1605	1.25 (t, 3 H, <i>J</i> = 7.1), 1.90 (s, 3 H), 4.09 (q, 2 H, <i>J</i> = 7.1), 4.41 (d, 2 H, <i>J</i> = 6.4), 4.53 (s, 1 H), 7.22–7.36 (m, 5 H), 8.95 (br s, 1 H)	14.76, 19.48, 24.20, 46.89, 58.50, 83.32, 126.83, 127.46, 128.90, 138.88, 162.12, 170.72
1g	-OCH ₂ CH ₃	-C ₆ H ₅	25	65	1644, 1589	1.28 (t, 3 H, <i>J</i> = 7.1), 1.98 (s, 3 H), 4.14 (q, 2 H, <i>J</i> = 7.1), 4.69 (s, 1 H), 7.05–7.34 (m, 5 H), 10.39 (br s, 1 H)	14.47, 20.18, 58.62, 85.93, 124.26, 124.78, 128.93, 139.22, 158.80, 170.28
1h^a	-OCH ₂ CH ₃	-CH ₂ CH ₂ NH ₂	0.5	95	1648, 1609	1.24 (t, 6 H, <i>J</i> = 7), 1.91 (s, 6 H), 3.34–3.37 (m, 4 H), 4.08 (q, 4 H, <i>J</i> = 7), 4.48 (s, 2 H), 8.65 (br s, 2 H)	14.73, 19.38, 43.95, 58.60, 83.71, 161.45, 170.75
1i^a	-CH ₃	-CH ₂ CH ₂ OH	14	87	1609, 1572	1.96 (s, 3 H), 1.97 (s, 3 H), 3.40 (q, 2 H, <i>J</i> = 5.4), 3.75 (t, 2 H, <i>J</i> = 5.4), 4.42 (br s, 1 H), 4.97 (s, 1 H), 10.84 (br s, 1 H)	19.14, 28.55, 45.46, 61.35, 95.63, 164.06, 194.81
1j	-CH ₃	CH ₂ CH=CH ₂	9	74	1613, 1574	1.91 (s, 3 H), 2.00 (s, 3 H), 3.86 (br s, 2 H), 5.01 (s, 1 H), 5.16 (d, 1 H, <i>J</i> = 11.1), 5.21 (d, 1 H, <i>J</i> = 18.2), 5.79–5.91 (m, 2 H), 10.87 (br s, 2 H)	18.08, 28.36, 44.62, 95.18, 115.56, 133.64, 162.73, 194.54
1k	-CH ₃	- <i>c</i> -C ₆ H ₁₁	6	88	1606, 1577	1.27–1.86 (m, 10 H), 1.95 (s, 3 H), 1.98 (s, 3 H), 3.34–3.38 (m, 1 H), 4.91 (s, 1 H), 11.00 (br s, 1 H)	18.25, 24.07, 24.99, 28.34, 33.46, 51.13, 94.59, 161.56, 193.91

Table (continued)

Entry	R	R ¹	Reaction Time (h)	Yield (%) ^b	IR ν (cm ⁻¹) ^c	¹ H NMR (300 MHz, CDCl ₃) δ (ppm), <i>J</i> (Hz) ^d	¹³ C NMR (75 MHz, CDCl ₃) δ (ppm) ^d
1l^a	-CH ₃	-C ₆ H ₅	24	60	1610, 1587	1.99 (s, 3 H), 2.10 (s, 3 H), 5.19 (s, 1 H), 7.08–7.36 (m, 5 H), 12.48 (br s, 1 H)	19.75, 29.08, 97.53, 124.66, 125.47, 129.01, 138.66, 160.16, 196.06
1m^a	-CH ₃	-CH ₂ CH ₂ NH ₂	10	60	1613, 1580	1.84 (s, 6 H), 1.92 (s, 6 H), 3.34–3.37 (m, 4 H), 4.92 (s, 2 H), 10.82 (br s, 2 H)	18.41, 28.58, 43.24, 95.87, 162.63, 195.16
1n^a	-C ₆ H ₅	-CH ₂ CH ₂ OH	4	78	1598, 1547	1.99 (s, 3 H), 3.44 (q, 2 H, <i>J</i> = 5.4), 3.79 (t, 2 H, <i>J</i> = 5.4), 5.63 (s, 1 H), 7.35–7.41 (m, 3 H), 7.80–7.84 (m, 2 H)	19.58, 45.66, 61.48, 92.64, 126.90, 128.17, 128.32, 130.50, 140.32, 165.80, 187.67
1o	-C ₆ H ₅	CH ₂ CH=CH ₂	10	71	1595, 1543	2.03 (s, 3H), 3.89–3.94 (m, 2 H), 5.19 (d, 1 H, <i>J</i> = 10.4), 5.26 (d, 1 H, <i>J</i> = 17.1), 5.70 (s, 1 H), 5.81–5.95 (m, 1 H), 7.33–7.40 (m, 3 H), 7.82–7.89 (m, 2 H), 11.48 (br s, 1 H)	19.13, 45.35, 92.38, 116.44, 126.89, 128.14, 130.46, 133.72, 140.34, 165.03, 187.86

^aSolid products, mp (°C): 126 (**1h**), 72 (**1i**), 47 (**1l**), 105 (**1m**), 81 (**1n**).

^bIsolated yields.

^cCarbonyl and hydrogen-bonded carbonyl signals. Measured on a FT-IR Hewlett Packard.

^dRecorded on a Bruker DPX 300 NMR spectrometer.

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