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# A New Route to α-Hetero β-Enamino Esters using A Mild and Convenient Solvent-Free Process Assisted by Focused Microwave Irradiation

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**Abstract** : New α-hetero β-enamino esters **5** (X = NH, O, S) are obtained in good to excellent yields by transamination reactions from ethyl 3-dimethylamino acrylate **2(a-c)** and various volatile amines **3(a-e)** using solvent-free conditions assisted by focused microwave irradiation. Most of the α-hetero β-enamino ester derivatives **3** present a (E)-s-*cis/trans* conformation. 

Microwave-assisted organic synthesis have recently received considerable attention from synthetic chemists because of their high efficiency, environmentally benign conditions and convenient work-up conditions[1]. One of the most useful implementations of organic synthesis under microwave irradiation is the so-called *solvent-free*[2] or *dry media*[3] synthesis. Recently, Khmelnitsky *et al.*[4] have extended the use of microwave technology in combinatorial chemistry for the synthesis of a library of substituted pyridines using bentonite clay as solid support[5].

One of the continuing aim of our laboratory is to develop new synthetic routes to five-membered heterocycles by [3+2] cycloadditions reactions using solvent-free conditions[6] and to condensed heterocycles from heterocyclic ketene aminal by tandem reactions under focused microwave irradiation[7]. In connection with our general interest in annelation of benzimidazoles derivatives with β-dielectrophiles[8], we recently reported the preparation of ethyl 1-oxo-1,2-dihydropyrimido-[1,6-a]-benzimidazole-4-carboxylate[9] using solvent-free conditions. The benzimidazole scaffold is an essential structural element of various drugs including antirhino/enteroviral agents[10].

In view of the great utility of β-enamino esters[11] as versatile intermediates in the asymmetric synthesis[12] of β-lactam antibiotics[13], alkaloids[14] and non-benzodiazepine heterocycles[15], it may be worthwile to explore the reactivity of the 3-dimethylamino acrylate derivatives **2(a-c)** in transamination reactions with various volatile amines. In this paper, we describe results that sucessfully led to the development of a simple method for the synthesis of new α-hetero β-enamino esters by a solvent-free process assisted by focused microwave technology.

The starting ethyl 3-dimethylamino-acrylate derivatives **2(a-c)** were easily prepared in good yields without solvent from a mixture of the respective compounds **1a**[16], **1b**[17] or **1c**[17] and N,N-dimethylformamide diethylacetal[18a] (DMF-DEA) at 90°C during 15 minutes under focused microwave irradiation[19] (Scheme 1). The structure of **2(a-c)** was assigned on the basis of spectral data ($^1$H NMR) in agreement with the literature[20].

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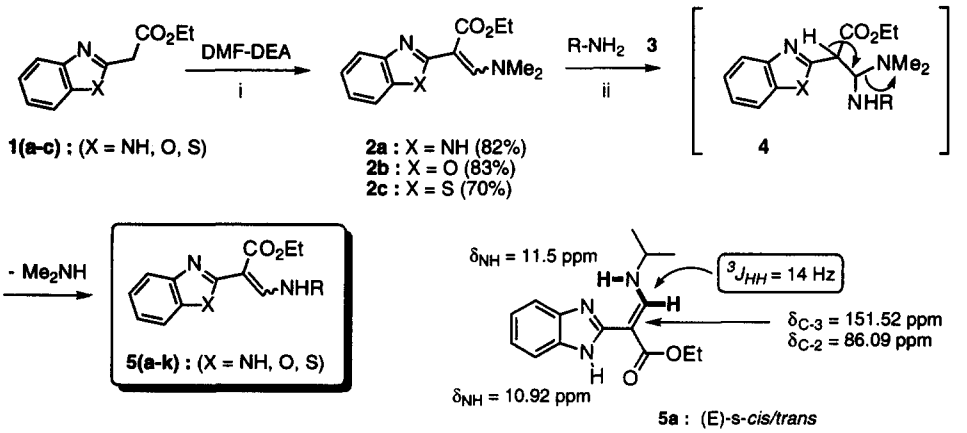


(i) : μω (Synthewave® 402 reactor), 90°C, 15 min. (ii) : μω, 30 min.

**3a** : R = $Me_2CH$; **3b** : R = $Me_3C$; **3c** : R = Et(Me)CH; **3d** : R = $CH_3CH_2CH_2$; **3e** : R = $(EtO)_2CHCH_2$.

**Scheme 1**

**Table 1** : Synthesis of α-hetero β-enamino esters **5(a-k)** from amines **3(a-e)** and 3-dimethylamino acrylates **2(a-c)**

| Amine | R | Product | X | Temperature (°C)[a] | Yield (%)[b] | *ratio* E/Z[c] |
|---|---|---|---|---|---|---|
| **3a** | $Me_2CH$ | **5a** | NH | 30 | 94 | 100 : 0 |
| **3b** | $Me_3C$ | **5b** | " | 40 | 97 | " |
| **3c** | Et(Me)CH | **5c** | " | 60 | 98 | " |
| **3d** | $CH_3CH_2CH_2$ | **5d** | " | 40 | 98 | " |
| **3a** | $Me_2CH$ | **5e** | O | 30 | 95 | 90 : 10 |
| **3b** | $Me_3C$ | **5f** | " | 40 | 97 | - |
| **3c** | Et(Me)CH | **5g** | " | 60 | 93 | 90 : 10 |
| **3d** | $CH_3CH_2CH_2$ | **5h** | " | 40 | 94 | 93 : 7 |
| **3e**[d] | $(EtO)_2CHCH_2$ | **5i** | " | 95 | 95 | 95 : 5 |
| **3b** | $Me_3C$ | **5j** | S | 40 | 90 | 100 : 0 |
| **3d** | $CH_3CH_2CH_2$ | **5k** | " | 40 | 93 | " |

[a] Temperature measured in the focused microwave reactor[19b]. [b] Yield of isolated product. [c] Calculated from $^1H$ NMR spectra of the crude reaction mixture ($CDCl_3$, Bruker AC 300P, TMS as internal ref.).[d] Reaction realized with a ratio of **3e/2b** : 1/1.

Following our investigations of the chemical reactivity of 3-dimethylamino acrylate derivatives **2(a-c)**, we used various volatile amines **3** (excepted for **3e** : R = $(EtO)_2CHCH_2$) using solvent-free technique. The great advantage of this method is that it can be eventually conducted in open vessels, making it simple and safe to perform. Several experiments were performed, at various powers and irradiation times, in order to find the most adequate conditions for the reaction under microwave irradiation. In a typical experiment, compound **1** (80 mmoles) was mixed with an excess of amine **3** (1.5 mL) in the microwave reactor (Ø = 4 cm). Then, the mixture was immediately submitted to focused microwave irradiation at the suitable temperature[19b] during 30 minutes[21] (Table 1). Extraction of the reaction mixture from the microwave reactor with 15 mL of methylene

chloride, elimination of solvent and excess of **3** *in vacuo* followed by the analysis of the crude reaction mixture by $^1$H NMR spectroscopy indicate the formation of the desired compound **5**. In this process, the mechanism is an addition-elimination[18b] after the loss of dimethylamine from the aminal intermediate **4** which could not be isolated (Scheme 1). The expected compounds **5(a-k)** were purified by recrystallization. As can be seen from Table 1, the new β-enamino esters **5(a-k)** are synthetized in good yields according to this procedure.

β-Enamino esters **5(a-d)** derived from **2a** and **3(a-d)** adopt the (E)-s-*cis/trans* conformation (see **5a**[22] in Scheme 1), stabilized by hydrogen bond as indicated by a strongly downfield shifted resonance of the amino group on C-3 (δ = 11.5 ppm in the $CDCl_3$ $^1$H NMR spectrum). The presence of a coupling constant ($^3J$ = 14 Hz) between the amino proton and H-3 ($\delta_{H\text{-}3}$ = 8.08 ppm) indicates a *trans*-relationship[23]. The shift of NH for benzimidazol-2-yl group ($\delta_{NH}$ = 10.92 ppm) accounts for an intramolecular hydrogen bond.

We have also found that the C-2/C-3 bond revealed a strong polarization (**5a** : $\delta_{C\text{-}3}$ = 151.52 and $\delta_{C\text{-}2}$ = 86.09 ppm) as a consequence of a "push-pull" effect[24]. The shift of C-2 is confirmed in the $^1$H resonance-coupled $^{13}$C NMR spectra by identification of a doublet centered at δ = 86.09 ppm with a small coupling constant between C-2 and H-3 ($^2J$ = 2.1 Hz).

β-Enamino esters **5(j,k)** obtained respectively from amines **3b** and **3d**, and ethyl 2-(1*H*-benzothiazol-2-yl)-3-dimethylamino acrylate **2c** also presents a (E)-s-*cis/trans* conformation but the products **5(e-i)** derived from ethyl 2-(1*H*-benzoxazol-2-yl)-3-dimethylamino acrylate **2b** appear in the $^1$H NMR spectrum as a mixture of two conformers (Table 1).

To summarize, we have developed a useful and versatile new access to β-enamino esters using a solvent-free process assisted by focused microwave technology from easily accessible starting materials. To our knowledge, these transamination reactions have never been reported and this procedure may complement those existing in the literature for the synthesis of β-enamino esters. The products **5(a-d)** derived from ethyl 2-(1*H*-benzimidazol-2-yl)-3-dimethylamino-acrylate **2a** and **5(j,k)** derived from ethyl 2-(1*H*-benzothiazol-2-yl)-3-dimethylamino-acrylate **2c** with a (E)-s-*cis/trans* conformation could also find applications in asymmetric reduction reactions[12]. Work is now in progress to study the potentialities of these reactions.

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(21) When the same reaction mixture was heated in an oil bath previously set at the same boiling point for the same reaction time, the results were analogous. In these cases, we can exclude a specific microwave effect.

(22) *Selected spectral data of* ethyl 3-methylethylamino 2-(1*H*-benzimidazol-2-yl)acrylate (**5a**) : $^1$H NMR ($CDCl_3$, 300 MHz) δ : 1.36 (t, J = 7.2 Hz, 3H); 1.40 (d, J = 6.6 Hz, 6H); 3.70 (hept, J = 6.6 Hz, 1H); 4.29 (q, J = 7.2 Hz, 2H); 7.16-7.20 (m, 2H, Ar); 7.35-7.40 (dd, 1H, Ar); 7.58-7.62 (dd, 1H, Ar); 8.08 (d, J = 14 Hz, 1H, H-3); 10.92 (broad s, 1H, NH); 11.50 (broad s, 1H, NH), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ : 14.65 (qt, J = 127, 2.4 Hz); 23.78 (qm, J = 127 Hz); 50.79 (dq, J = 138, 4.4 Hz); 59.67 (tq, J = 147, 4.3 Hz); 86.09 (d, J = 2.1 Hz, C-2); 110.13 and 117.34 (ddd, J = 161, 6.1 Hz, C-5', C-6'); 121.29 and 121.46 (dd, J = 161, 8.1 Hz, C-4', C-7'); 131.82 and 142.33 (sm, C-3a', C-7a'); 151.52 (dd, J = 167, 3.8 Hz, C-3); 152.87 (sdd, J = 9.6 Hz, C-2'); 168.19 (sm, C-1), I.R. ($cm^{-1}$, nujol) 3380, 1650, 1600; HRMS, *m/z* = 273.1485 found (calculated for $C_{15}H_{19}N_3O_2$ requires 273.1477); mp = 132-134°C.

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