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Article

The Solvent Free Preparation of β-Amino Esters α,β-Unsaturated Ketones and Esters with Domestic Microwave Oven

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Uma série de cetonas e ésteres α,β-insaturados β-amino ésteres, **4a**-**h** e **6a**-**d**, derivados de α-amino ácidos foi obtida a partir dos cloridratos dos α-amino ésteres **2a**-**d** e dos compostos 1,3-dicarbonílicos **3a**,**b** e **5** em presença de trietilamina. Estes compostos foram preparados empregando energia de microondas, sem uso de solvente, utilizando como suporte sólido K-10 ou KSF e também foram efetuadas reações na ausência de suporte sólido.

A series of β-amino esters α,β-unsaturated ketones and esters **4a**-**h** and **6a**-**d** derived from α-amino acids have been prepared starting from α-amino esters hydrochorides **2a**-**d** with 1,3-dicarbonyl compounds **3a**,**b** and **5** in presence of triethylamine. These compounds have been prepared under domestic microwave oven, under solvent free condition with and without solid support (K-10 or KSF).

Keywords: α-amino acids, solid support, microwave, α-amino esters

Introduction

We have recently investigated the use of microwave radiation in the preparation of β-enamino carbonylic compounds in reactions using solid support, K-10, under solventless conditions.[1,2] The use of solventless conditions with heterogeneous media in domestic microwave ovens is an useful alternative and has received considerable attention due to its greater efficiency from an economic as well as an ecological point of view.[3]

Continuing our investigations exploring this methodology, we report herein the preparation of β-amino esters α,β-unsaturated ketones and esters **4a**-**h** and **6a**-**d**. The β-enamino carbonylic compounds and the compounds described in this work are of interest as chemical intermediates for a variety of heterocyclic compounds with pharmacological properties, such as oxazolidinones**,** pyrrole and α- amino -β lactams.[4-9]

In this work the β-amino esters α,β-unsaturated ketones and esters **4a**-**h** and **6a**-**d** were prepared by reaction of α-amino esters **2a**-**d** and 1,3-dicarbonyl compounds **3a**,**b** or **5** with microwave irradiation and organic solvent free condition using solid support, K-10 or KSF, in order to compare the acid characteristic of these supports. The use of potassium fluoride (KF), as an anionic support, with microwaves has been mentioned in the literature to prepare β-amino esters α,β-unsaturated ketones trought the reaction only with α-amino esters derivated of glycine, L-alanine, and L-proline and acetylacetone.[10] We also tested these reactions without solid support.

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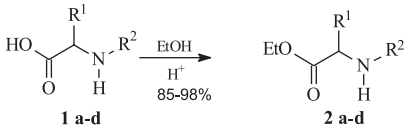
Results and Discussion

The strategy used to obtain the compounds **4a**-**h** and **6a**-**d**, proceeded in a first step with the protection of the α-amino acids.[11] This protection was made necessary due to the prototropy observed between the carboxylic group and the amino group of the α-amino acids. α-amino esters hydrochlorides were prepared from α-amino acid **1a**-**d** glycine, L-alanine, L-serine and L-proline respectively in EtOH with thionyl chloride as catalyst, with these conditions the protected compounds **2a**-**d** were isolated in excellent yield (Scheme 1).



2	a	b	c	d
R^1	H	Me	$-CH_2OH$	$-(CH_2)_3-$
R^2	H	H	H	

Scheme 1.

For the preparation of β-amino esters α,β-unsaturated ketones and esters **4a**-**h** we used the reaction of α-amino esters **2a**-**d** and acetylacetone **3a** or ethyl acetoacetate **3b** with 1 equiv. of triethylamine supported in K-10 or KSF with microwave irradiation without solvent, Scheme 2. The compounds **4a**-**h** were obtained in good yield (see Table 1).

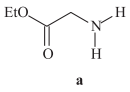
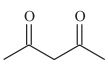
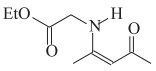
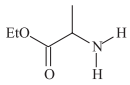
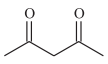
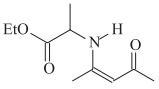
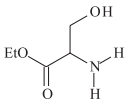
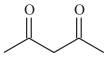
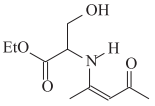
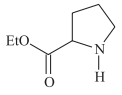
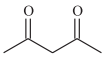
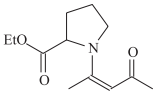
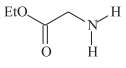
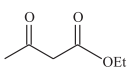
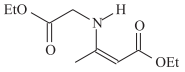
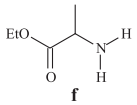
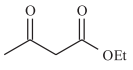
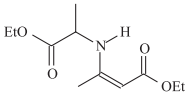
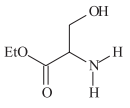
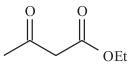
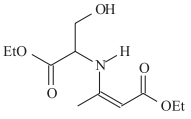
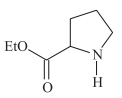
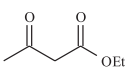
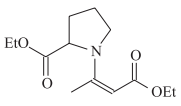
Montmorillonite, especially K-10, has been used as an efficient acid catalyst in our laboratories to obtain β-enamino carbonylic compounds.[12-14] The use of K-10 or KSF as solid support avoids the use of the organic acids that favour the formation of by-products or cause the hydrolysis of the enamino carbonylic compounds.

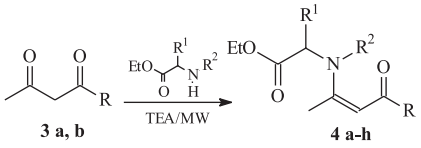
Due to the Brönsted acid nature K-10 or KSF[15] and the possible interaction with polar compounds, we decided investigate these reactions without solid supports, using only microwave irradiation. We observed that **4a**-**h** was obtained in excellent yield, Table 1.

To evaluate if the acidic nature of the solid supports (K-10 or KSF) and the temperature could affect the optical purity of the chiral compouds that were obtained, we chose the compoud **4b**, derivative of L-alanine. This compound was analyzed by GC (Gas Chromatography) with a chiral column and independent of the employed methodology (MW, MW/K-10 or MW/KSF), 95.7% of optical purity was obtained.

The good results obtained for the preparation of the acyclic β-amino esters α,β-unsaturated ketones and esters **4a**-**h** encouraged us to extend this methodology to obtain cyclic α,β-unsaturated β-amino esters compounds with cis-*s*-*cis* configuration.

Table 1. β-amino esters α,β-unsaturated Ketones and Esters **4a**-**h** prepared

Aminoester **2**	Dicarbonylic **3**	Product **4**	Yield (%); time (min) MW	MW/K-10	MW/KSF	mp (º C)
 **a**			80; 3	67; 3	64; 3	65-66
 **b**			93; 3	57; 3	62; 3	oil
 **c**			50; 1	36; 2	46; 2	78-80
 **d**			70: 3	60; 3	60; 3	oil
 **e**			95; 3	66; 3	64; 3	50-51
 **f**			86; 3	68; 3	78; 3	oil
 **g**			84; 1	50; 2	45; 2	70-71
 **h**			67; 3	62; 3	65; 3	66-67



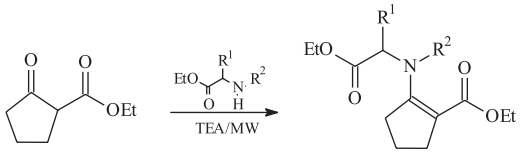
3 a, b 4 a-h

4	a	b	c	d	e	f	g	h
R	Me	Me	Me	Me	OEt	OEt	OEt	OEt
R^1	H	Me	$-CH_2OH$	$-(CH_2)_3-$	H	Me	$-CH_2OH$	$-(CH_2)_3-$
R^2	H	H	H		H	H	H	

Scheme 2.

The ethyl-2-oxo-1-cyclopentanecarboxylate **5** used as dicarbonyl compound was obtained in agreement with the literature procedure, from diethyl adipate.[16] The reaction occurs through Dieckmann cyclization, employing anhydrous aluminium trichloride and triethylamine in dichloromethane at room temperature.

Compounds **6a-d** were obtained in excellent yield by reacting the dicarbonyl compound **5** dispersed on solid support (K-10 or KSF) with α-amino esters hydrochloride **2a-d**. These compounds were obtained in excellent yield with and without solid support (see Scheme 3 and Table 2). Triethylamine was used to reform the free amino ester and permit the attack of the nitrogen atom on the carbonyl group. When this reaction was performed without triethylamine the starting material was recovered. The structures of the products were unambiguously established based on the ^1H and ^{13}C NMR spectra experiments (Table 3).



5 6 a-d

6	a	b	c	d
R^1	H	Me	$-CH_2OH$	$-(CH_2)_3-$
R^2	H	H	H	

Scheme 3.

Conclusions

In conclusion, we describe in this work a facile method to obtain enamines derived from α-amino acids by reactions without solvent in open glass vessels using a

Table 2. β-amino esters α,β-unsaturated Esters **6a-d** prepared

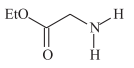
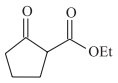
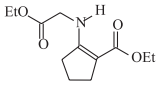
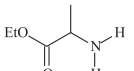
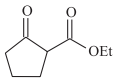
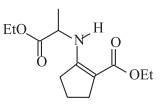
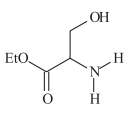
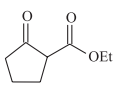
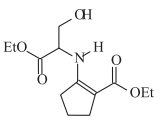
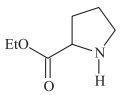
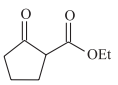
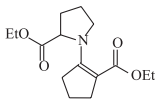
Aminoester **2**	Dicarbonylic **5**	Product **6**	Yield (%); time (min) MW	MW/K-10	MW/KSF	mp (° C)
 **a**			80; 3	81; 3	90; 3	68-70
 **b**			86; 3	86; 3	94; 3	oil
 **c**			50; 3	50; 3	50; 3	40-42
 **d**			93; 3	70; 3	70; 3	oil

Table 3. β-amino esters α,β-unsaturated Ketones and Esters **4a**-**h** and **6a**-**d** prepared

Product	^{1}H NMR ($CDCl_3$/TMS) δ, *J*(Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
4a	1.09 (t, 3H, *J* 7.1), 1.70 (s, 3H), 1.82 (s, 3H), 3.80 (d, 2H, *J* 6.2), 4.02 (q, 2H, *J* 7.1), 4.88 (s, 1H), 10.66 (br,1H)	14.1, 18.7, 28.9, 44.7, 61.5, 96.6, 161.9, 169.1, 196.0
4b	1.27 (t, 3H, *J* 7.5), 1.49 (d, 3H, *J* 7.04), 1.91 (s, 3H), 2,00 (s, 3H), 4.15-4.27 (m, 3H), 5.03 (s, 1H); 10.90 (br,1H)	13.6, 17.4, 18.2, 28.3, 50.9, 60.9, 95.9, 160.9, 171.6, 195.0
4c	1.29 (t, 3H, *J* 7.1), 1.94 (s, 3H), 1.98 (s, 3H),3.94 (d, 2H, *J* 5.1), 4.20 (q, 2H, *J* 7.1), 4.25-4.30 (m, 1H); 5.00 (s, 1H), 10.97 (br,1H)	14.0, 19.0, 28.6, 58.4, 61.6, 63.2, 96.7, 162.3, 169.9, 195.6
4d	1.28 (t, 3H, *J* 7.2), 1.98-2.29 (m,7H), 2.46 (s,3H), 3.22-3.68 (m,2H), 4.10-4.45 (m,3H), 5.00 (s,1H)	13.9, 16.6, 22.9, 30.1, 31.3, 48.3, 60.3, 61.1, 96.3, 172.0, 194.5
4e	1.24 (t, 3H, *J* 7.2), 1.29 (t, 3H, *J* 7.2), 1.90 (s, 3H), 3.99 (d, 2H, *J* 6.2), 4.10 (q, 2H, *J* 7.2), 4.22 (q, 2H, *J* 7.2), 4.56 (s, 1H), 8.81 (br,1H)	13.9, 14.3,18.9, 44.5, 58.2, 61.2, 84.3, 160.3, 169.6, 170.0
4f	1.25 (t, 3H, *J* 7.2), 1.28 (t, 3H, *J* 7.2), 1.47 (d, 3H, *J* 6.8),1.89 (s, 3H), 4.09 (q, 2H, *J* 7.2),4.15-4.23 (m, 3H), 4.52 (s, 1H), 8.75 (br,1H)	13.9, 14.3, 19.0, 19.1, 51.2, 58.2, 61.1, 84.3, 159.7, 170.0, 172.5
4g	1.24 (t, 3H, *J* 7.1), 1.29 (t, 3H, *J* 7.1), 1.92 (s, 3H), 2.85 (br,1H), 3.88-3.96 (m, 2H), 4.09 (q, 2H, *J* 7.1),4.19-4.26 (m, 3H), 4.57 (s, 1H); 8.9 (br,1H)	14.0, 14.4 ,19.5, 57.7, 58.6, 61.7, 63.5, 85.2, 160.2, 170.4, 170.6
4h	1.28 (t, 3H, *J* 7.1), 1.33 (3H, t, CH_3, *J* 7.1), 2.04-2.36 (m, 4H), 2.46 (s,3H), 3.40-3.51 (m, 2H), 4.10 (q, 2H, *J* 7.1), 4.25 (q, 2H, *J* 7.1), 4.36-4.38 (m,1H),4.55 (s, 1H)	13.6, 14.1, 15.7, 22.7, 29.9, 47.9, 57.6, 60.0, 60.6, 85.2, 158.0 , 168.2, 172.0
6a	1.26 (t, 3H, *J* 7.1),1.27 (t, 3H, *J* 7.1),1.82 (qui, 2H,*J* 7.4), 2.49-2.54 (m, 4H), 3.95 (d, 2H, *J* 6.3), 4.13 (q, 2H, *J* 7.1), 4.20 (q, 2H, *J* 7.1), 7.57 (br,1H)	13.6, 14.1, 20.2, 28.8, 31.5, 45.6, 58.0, 60.7, 94.3, 160.4, 167.5, 169.7
6b	1.27 (t, 3H, *J* 7.2), 1.45 (t, 3H, *J* 7.2), 1.82 (qui, 2H, *J* 7.3), 2.51 (t, 4H), 4.06 (qui,1H, *J* 6.0),4.14 (q, 2H, *J* 7.2), 4.19 (q, 2H, *J* 7.2), 7.57 (br,1H)	13.8, 14.3, 19.2, 20.5, 28.8, 31.7, 52.6 , 58.2, 60.9, 94.6, 162.0, 167.8, 172.6
6c	1.27 (t, 3H, *J* 7.1), 1.28 (t, 3H, *J* 7.1), 1.83 (qui, 2H, *J* 7.4), 2.48-2.54 (m, 4H), 2.93 (br,1H), 3.87 (d, 2H, *J* 6.4), 4.09 (m, 1H), 4.14 (q, 2H, *J* 7.1), 4.22 (q, 2H, *J* 7.1), 7.73 (br,1H)	14.0, 14.5, 20.7, 29.2, 32.2, 58.7, 59.5, 61.7, 63.6, 95.7, 162.5, 168.3, 170.8
6d	1.29 (t, 6H, *J* 7.2), 1.75-1.99 (m, 2H), 2.09-2.20 (m,2H), 2.25-2.36 (m, 6H), 3.11 (t, 2H), 4.15-4.22 (m,5H)	14.0, 14.4, 20.6, 23.5, 30.5, 30.7, 36.7, 51.6, 58.5, 60.7, 62.6, 96.1, 157.4; 165.7, 175.1

domestic MW with good to excellent yield. We believe that this procedure is an attractive addition to the existing methodologies to obtain synthons for asymmetric synthesis of heterocyclic compounds using cleaner methodologies with reduced time of reaction.

Experimental

Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer in deuteriochloroform/tetramethylsilane. Microwave irradiations were carried out in a SANYO EM-700T domestic oven (700 W). The solid support K-10 (Fluka) and KSF (Aldrich) were used. The temperature at the end of the experiment on the MO was between 70 and 80 °C as determined by the melting points of compounds **4c** and **4g**.

*α-Amino esters **2a**-**d**. General procedure*

To ethanol (100 mL) previously cooled at -20° C, was added dropwise thionyl chloride (26 mL; 35.6 mmol), after the α-amino acid (100 mmol) was added, a suspension was observed. The reaction mixture was stirred at room temperature until not being observed the suspension. The solvent was evaporated in vacuum and the residue was dissolved in ethanol and precipitated with ethyl ether, the salt was collected by filtration and washed with ether to give the α-amino esters hydrochlorides **2a**-**c** solids, except for **2d** which is oil.

Typical procedure with K-10 or KSF

Acetylacetone **3a** or ethyl acetoacetate **3b** or ethyl cyclopentanecarboxylate **5** (5 mmol) and α-amino esters **2 a**-**d** (7.5 mmol to obtain **4** and 10 mmol for 6 were used) with 1 equiv. of triethylamine were dispersed on K-10 or KSF (1.5 g). The heterogeneous mixture was submitted to microwave irradiation at 155 W for the time described in Table1 and Table 2. The products were extracted by washing the K-10 or KSF with ethyl acetate. The organic layer was washed with water, dried with $MgSO_4$, filtered and the solvent was removed under vacuum to give **4a**-**h** and **6a**-**d**.

Typical procedure without K-10 or KSF

Acetylacetone **3a** or ethyl acetoacetate **3b** or ethyl cyclopentanecarboxylate **5** (5 mmol) and α-amino esters **2a-d** (7.5 mmol to obtain 4 and 10 mmol for 6 were used) with 1 equiv. triethylamine were submitted to microwave irradiation for 1-3 min. (see Table 1 e Table 2) at 155 W. After the reaction mixture was cooled at room temperature and was added ethyl acetate. The organic layer was washed with water, dried with $MgSO_4$, filtered and the solvent was removed under vacuum to give **4a-h** and **6a-d**.

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