Synthesis and Reactivity of β-Amino α,β-Unsaturated Ketones and Esters Using K-10 Montmorillonite

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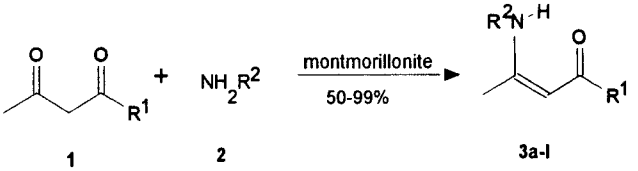
Received 17 December 1993; revised 9 March 1994

A series of β-amino α,β-unsaturated ketones **3a–f** and esters **3g–l** may be conveniently prepared by dispersing ammonia (NH_4OH solution), primary amines and 1,3-diketones or 1,3-keto esters on K-10 montmorillonite without solvent. This procedure was also applicable to the reactions of **3a** and **3g** with phenyl isocyanate and phenyl isothiocyanate which afford selectively the *C*-adducts **4a–d**.

The use of supported reagents in organic synthesis has increased for a variety of reactions.[1,2] Recent studies in our laboratory[3] have been directed toward the development of methodologies suitable for syntheses and reactivity studies of β-amino α,β-unsaturated ketones and esters using alumina (neutral) and montmorillonite K-10 as solid support. For these compounds, montmorillonite has been proved more efficient than alumina. The most usual preparation of β-amino α,β-unsaturated ketones and esters involves the direct reaction of a β-dicarbonylic compound with the amine in an aromatic solvent with azeotropic removal of water formed.[4] Other methods are known for the preparation of these compounds: (i), condensation of primary aromatic amines with β-keto esters utilizing montmorillonite K-10 as acid catalyst in benzene;[5,6] (ii), reaction of benzylamine with β-keto esters in heterogeneous media with alumina or montmorillonite as solid support;[7] or (iii), by hydrogenation (Raney-Ni) of isoxazoles.[8] When low boiling amines are used, special conditions are necessary, e.g., operating in an autoclave or applying elevated temperatures.[9] Under these conditions, yields are not quantitative, and byproducts can be formed, which are often difficult to separate. In this work we describe a selective method using montmorillonite K-10 as solid support, to obtain a series of β-amino α,β-unsaturated ketones **3a–f** and esters **3g–l** in good yields under simple and mild conditions.



3	R^1	R^2	3	R^1	R^2
a	Me	H	g	OEt	H
b	Me	Me	h	OEt	Me
c	Me	i-Pr	i	OEt	i-Pr
d	Me	t-Bu	j	OEt	t-Bu
e	Me	Ph	k	OEt	Ph
f	Me	Bn	l	OEt	Bn

Scheme 1

Table 1. β-Amino α,β-Unsaturated Ketones **3** Prepared

Product	Yield (%)	mp (°C) or bp (°C)/Torr	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
3a	87	33–35[a]	1.91 (s, 3H), 2.02 (s, 3H), 5.02 (s, 1H)	29.02, 95.52, 22.03, 161.22 (q), 196.47 (q)
3b	90	37–39[a]	1.91 (s, 3H), 1.98 (d, 3H, *J* = 5.6), 2.92 (d, 3H, *J* = 5.6)	18.24, 28.30, 29.05, 94.77, 163.80 (q), 194.24 (q)
3c	81	98/20	1.23 (d, 6H, *J* = 6.3), 1.94 (s, 3H), 1.98 (s, 3H), 3.71 (m, 1H, *J* = 6.3), 4.90 (s, 1H), 10.82 (br, 1H)	18.23, 23.55, 28.41, 44.29, 94.57, 161.46 (q), 194.14 (q)
3d	60	145/20	1.40 (s, 9H), 1.98 (s, 3H), 2.05 (s, 3H), 4.89 (s, 1H), 11.35 (br, 1H)	20.35, 28.59, 30.74, 52.19 (q), 96.20, 163.21 (q), 193.87 (q)
3e	77	49–50	1.98 (s, 3H), 2.09 (s, 3H), 5.18 (s, 1H), 7.03–7.43 (m, $5H_{arom}$), 12.47 (br, 1H)	19.60, 28.94, 97.45, 124.30, 125.35, 128.90, 138.60 (q), 159.98 (q), 195.87 (q)
3f	99	134/0.05	1.89 (s, 3H), 2.01 (s, 3H), 4.43 (d, 2H, *J* = 6.3), 5.03 (s, 1H), 7.27 (m, 5H), 11.12 (br, 1H)	18.70, 28.75, 46.60, 95.79, 126.58, 127.28, 128.68, 137.95 (q), 162.90 (q), 195.21 (q)
3g	90	106/20	1.24 (t, 3H, *J* = 7.2), 1.89 (s, 3H), 4.09 (q, 2H, *J* = 7.2), 4.49 (s, 1H)	14.39, 22.06, 58.30, 83.85, 159.86 (q), 170.08 (q)
3h	87	108/20	1.22 (t, 3H, *J* = 7.2), 1.90 (s, 3H), 2.89 (d, 3H, *J* = 7.2), 4.06 (q, 2H, *J* = 7.2), 4.44 (s, 1H)	14.10, 18.4, 28.69, 57.57, 81.46, 162.19 (q), 170.04 (q)
3i	90	138/20	1.19 (d, 6H, *J* = 4.8), 1.24 (t, 3H, *J* = 5.4), 1.93 (s, 3H), 3.70 (m, 1H, *J* = 4.8), 4.07 (q, 2H, *J* = 5.4), 4.38 (s, 1H), 8.45 (s, 1H)	14.51, 18.98, 23.96, 44.28, 57.97, 81.73, 160.60 (q), 170.43 (q)
3j	68	179/20	1.24 (t, 3H, *J* = 7.2), 1.37 (s, 9H), 2.04 (s, 3H), 4.08 (q, 2H, *J* = 7.2), 4.38 (s, 1H), 8.89 (s, 1H)	14.45, 20.69, 30.91, 51.66, 57.88, 83.36, 161.85 (q), 170.27 (q)
3k[6]	50	142/4	1.21 (t, 3H, *J* = 7.2), 1.93 (s, 3H), 4.09 (q, 2H, *J* = 7.2), 4.65 (s, 1H), 6.94–7.24 (m, 5H), 10.36 (br, 1H)	13.73, 57.81, 85.43 (q), 123.50, 124.02, 128.22, 138.62 (q), 157.94 (q), 169.49 (q)
3l	99	126/0.05	1.19 (t, 3H, *J* = 7.2), 1.81 (s, 3H), 4.05 (q, 2H, *J* = 7.2), 4.31 (d, 2H, *J* = 6.4), 4.52 (s, 1H), 7.12–7.27 (m, $5H_{arom}$), 8.95 (br, 1H)	14.15, 18.67, 46.21, 57.76, 82.87, 126.23, 126.82, 128.27, 138.43 (q), 161.16 (q), 170.00 (q)

[a] Purification by sublimation.

Table 2. Compounds **4a–d** Prepared[a]

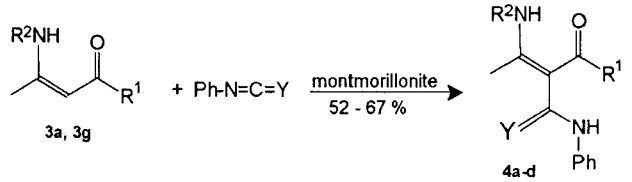
Product	Yield (%)	mp (°C)	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)	^{13}C NMR (DMSO-d_6/TMS) δ
4a	52	155–157	2.03 (s, 3H), 2.09 (s, 3H), 6.93–7.77 (m, 5H$_{arom}$), 10.10 (br, 1H)	20.03, 27.76, 108.62 (q), 119.34, 123.17, 128.62, 139.73 (q), 162.36 (q), 168.52 (q), 192.20 (q)
4b	67	148–150	2.02 (s, 3H), 2.10 (s, 3H), 7.21–7.98 (m, 5H$_{arom}$), 10.16 (br, 1H)	19.75, 27.28, 116.36 (q), 122.95, 125.98, 128.41, 139.90 (q), 159.73 (q), 190.81 (q), 199.93 (q)
4c	53	121–123	1.14 (t, 3H, J = 7.2), 2.09 (s, 3H), 4.06 (q, 2H, J = 7.2), 6.93–7.58 (m, 5H$_{arom}$), 11.16 (br, 1H)	14.21, 24.21, 59.15, 118.3 (q), 119.50, 122.57, 128.48, 139.71 (q), 151.19 (q), 167.51 (q), 169.05 (q)
4d	60	135–136	1.12 (t, 3H, J = 7.2), 2.01 (s, 3H), 4.01 (q, 2H, J = 7.2), 7.27–7.82 (m, 5H$_{arom}$), 11.46 (br, 1H)	14.42, 19.99, 58.44, 103.44 (q), 123.12, 125.62, 128.33, 140.19 (q), 159.16 (q), 166.45 (q), 198.00 (q)

[a] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.06, N ± 0.18, S ± 0.03; exception, **4d** N ± 1.09%.

Amines can also be applied in aqueous solution. Thus the stream of gaseous amine through the reaction vessel can be avoided as well as the use of solvents for removal of water. As can be seen in Scheme 1, the reaction also leads to good yields for molecules with bulky groups. The advantages of the procedure reported here are: (i), high purity of the products; (ii), high selectivity, and (iii), easy workup.

The good results obtained for β-enamino compounds using supported reactions without solvent stimulated us to utilize the same methodology in reactions with β-enamino compounds **3a** and **3g** and phenyl isocyanate or phenyl isothiocyanate. The β-enamino compounds reacted selectively to give *C*-acylated compounds: 4-amino-3-phenylaminocarbonyl-3-penten-2-one **(4a)** and 4-amino-3-phenylaminothiocarbonyl-3-penten-2-one **(4b)**, and ethyl 3-amino-2-phenylaminocarbonyl-2-butyrate **(4c)** and ethyl 3-amino-2-phenylaminothiocarbonyl-2-butyrate **(4d)**.

It has been reported that reactions of enamino compounds with phenyl isocyanates and isothiocyanates in homogeneous media yield mixtures of *N*- and *C*-adducts. The regiochemistry of these reactions depends on the *N*-amino substituent: reaction with the NH_2 group leads preferentially to *N*-acylated products, whereas reaction with the NHR-group (R = alkyl) yields *C*-acylated compounds predominantly.[10]



4	R^1	Y
a	Me	O
b	Me	S
c	OEt	O
d	OEt	S

Scheme 2

The acylation of **3a** and **3g** with phenyl isocyanate or phenyl isothiocyanate on montmorillonite K-10 gave selectively the *C*-acylated products **4–d** (Scheme 2, Table 2).

This was confirmed by ^{1}H NMR spectroscopy as the signal for the olefinic proton at the α-carbon atom of the β-enamino compound disappears.

Summarizing the results, a versatile method for the preparation of enamino compounds has been developed using easily accessible compounds.

Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AC-80 spectrometer (^{1}H at 80 MHz with TMS as internal standard and ^{13}C at 20 MHz). Elemental analyses were carried out on a Heraeus CHN-standard analyzer series 1958.

β-Amino α,β-Unsaturated Ketones and Esters 3a–l; General Procedure:

Amine **2** (12 mmol; for **3a**, 25% aq NH_4OH was used) was added dropwise to the dicarbonyl compound **1** (10 mmol) dispersed on montmorillonite K-10 (3 g; Fluka) and stirred at r.t. (except for **3d** and **3l** 60°C) for 24 h (for **3a,c,i** and **k** 5 h). The product was extracted by washing with CH_2Cl_2 (4 × 20 mL), dried ($MgSO_4$), and the solvent was removed in vacuo. For **3j**, the purification was performed by column chromatography on silica gel (Merck, 70–230 mesh) using hexane/EtOAc as eluent.

4-Amino-3-phenylaminothiocarbonyl-3-penten-2-one (4b); Typical Procedure:

Phenyl isothiocyanate (9.6 mmol) was added dropwise to the β-enamino compounds **3a** and **3g** (both 8 mmol) dispersed on montmorillonite K-10 (2 g; Fluka) and the mixture was stirred at 40°C for 15 h. The products were extracted by washing the montmorillonite with CH_2Cl_2 (4 × 20 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo to yield the crude products which were purified by recrystallization from diisopropyl ether to give **4** (Table 2).

The authors thank the financial support from the Conselho Nacional de Desenvolvimento Científico e tecnológico (CNPq), the Fundação de Amparo a Pesquisa do Estado do Rio Grande do Sul (FAPERGS), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and the Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ), and the fellowships from CNPq. Elemental analyses were provided by Dr. L. Wessjohann, University of Munich. The authors are grateful to B. Nagel for helpful comments on the manuscript.

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