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LETTER

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Efficient synthesis of β-amino-α,β-unsaturated carbonyl compounds†

Yuanhong Zhao, Jingfeng Zhao, Yongyun Zhou, Ze Lei, Liang Li and Hongbin Zhang*

School of Pharmacy, Center for Advanced Studies of Medicinal and Organic Chemistry, Yunnan University, Kunming, Yunnan, 650091, P. R. China. E-mail: zhanghb@ynu.edu.cn; Fax: 86-871-5035538; Tel: 86-871-5031119

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A versatile and high-yielding procedure for the synthesis of β-enamino esters and β-enaminones is presented: in the presence of tetraethyl orthosilicate, a number of highly functional β-enamino esters were obtained; this method provided an alternative for the formation of β-amino-α,β-unsaturated carbonyl compounds with mild and functional group compatible reaction conditions.

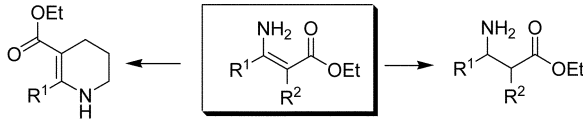
β-Enaminones and β-enamino esters are versatile intermediates for the synthesis of nitrogen containing compounds.[1] They are also important subunits present in some biologically important natural products as well as therapeutic agents.[2] Recent studies have revealed that some of the simple β-enaminones are biologically active and served as leads for antibacterial agent development.[3] Due to the importance of β-enaminone derivatives both as bioactive leads and as versatile building blocks, synthesis and application of β-enaminone and enamino esters have long been an active topic in organic synthesis. Although many synthetic methodologies lead to β-enaminone derivatives,[4] the most attractive protocol is obviously the direct condensation of 1,3-dicarbonyl compounds with amines. A practical approach towards the synthesis of β-enaminones was reported by Baraldi in 1983,[5] in which the target compounds were made by refluxing 1,3-dicarbonyl compounds with amine or ammonium acetate in the presence of acetic acid in benzene with azeotropic removal of water. Since then, several new protocols leading to β-enaminone derivatives, in which Al_2O_3,[6] SiO_2,[7] montmorillonite K10,[8] 1,3-diketonatoboron difluorides,[9] $NaAuCl_4$,[10] $Zn(ClO_4)_2$,[11] $Bi(OCOCF_3)_3$[12] and $CeCl_3 \cdot 7H_2O$[13] were used as catalysts or as reactants have been published. New synthetic tools such as using ultrasound[14] and microwave radiation[7a,15] for the preparation of β-enamino esters have also been studied.

As part of our ongoing project towards the synthesis of nitrogen containing compounds, we needed a general method for the synthesis of β-enamino esters, especially those with a free β-amino group. There are ample examples for the preparation of β-enamino esters with primary and secondary amines, however few efforts were made to synthesize β-enamino esters with a free β-amino group (compound **1**, Fig. 1). From a synthetic point of view, a free amino group in β-enamino esters is a much more valuable functional group for manipulation. Although Baraldi's procedure afforded β-enaminones in good yields by refluxing ammonium acetate with 1,3-diketones in benzene, it provided β-enamino esters in low yields when substituted β-keto esters were used instead of 1,3-diketones.[16] Other protocols such as stirring 1,3-dicarbonyl compounds with ammonium acetate (or 25% aqueous ammonia) in ethanol or methanol at room temperature or at reflux,[17] increasing the quantity of acetic acid while carrying out the reaction in benzene–AcOH or toluene–AcOH (5 : 1) at reflux[18] were also carried out. While those procedures provided simple 3-amino-but-2-enoic acid ethyl ester in good yields (70–95%), they failed to afford β-amino-α,β-unsaturated esters with both R^1 and R^2 being substituted by alkyl groups in a reasonable yield (see Table 1). Addition of Lewis acid [$Zn(ClO_4)_2$, $Mg(ClO_4)_2$ and $Bi(TFA)_3$] as catalysts to the ammonium acetate system were fruitless even though good results had been reported in the literature for the condensation of primary alkyl amines with 1,3-dicarbonyl compounds in the presence of those additives. Other methodologies such as addition of Al_2O_3, silica gel or montmorillonite K10 were also conducted, however all failed to afford good yields for those keto esters with two substituted groups.

In order to access β-enamino esters with a functional group at the carbon C-2 position in reasonable yield, dehydration agents such as molecular sieves, anhydrous $MgSO_4$ were also used in the reaction system, however, no substantial improvement was observed.

In the literature, tetraethyl orthosilicate had been used as a dehydration agent,[19] thus $Si(OEt)_4$ was added to the reaction system containing ammonium acetate and β-keto ester in ethanol. To our delight, the reaction proceeded well and afforded the desired β-amino-α,β-unsaturated esters in good yields. Different solvents were screened and it was found that commercial absolute ethanol was the solvent of choice. In the presence of tetraethyl orthosilicate (1–3 equiv.), high isolated yields were obtained with most substrates employed in this research.[20] The results are summarized in Tables 1 and 2. Most β-amino-α,β-unsaturated esters are fairly stable and could be kept at room temperature for a few days or even weeks. One of the enamino esters, namely 3-amino-3-phenyl-acrylic acid ethyl ester, was converted to β-amino acid (98% yield) by hydrogenation with PtO_2 (see compound **2** in Fig. 1, R^1 = Ph, R^2 = H).

This tetraethyl orthosilicate procedure could be extended to synthesize β-enamino esters or β-enaminones with aryl, primary amines (see Table 3). The advantages of this procedure



3: Tetrahydropyridine **1**: Enaminoesters 2: β-amino acid

Fig. 1 Nitrogen containing compounds from β-enamino esters.

† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/nj/b4/b419254k/

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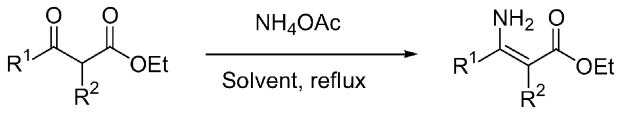
Table 1 Synthesis of β-enamino esters with a free β-amino group by different methods [a]



		Yield[b] (%)			
R^1	R^2	*A*	*B*	*C*	*D*
CH_3	$PhCH_2$	70	17	21	15
Ph	H	95	39	76	95
But-3-enyl	$CH_2 = CHCH_2$	95	<3	<5	<3

[a] *Method A*: Keto ester (1 mmol), NH_4OAc (4 mmol) and $Si(OEt)_4$ (2 mmol) in commercially available absolute ethanol (5 mL) were stirred at reflux; *Method B*: Keto ester (1 mmol), NH_4OAc (5 mmol) in commercially available absolute ethanol or methanol (5 mL) were stirred at reflux; *Method C*: Keto ester (1 mmol), NH_4OAc (5 mmol) and acetic acid (0.1 mL) in benzene (5 mL) were stirred at reflux with azetropic removal of water. *Method D*: Keto ester (1 mmol), NH_4OAc (10 mmol) and acetic acid (1 mL) in benzene (5 mL) were stirred at reflux. [b] Yields represented isolated yields. All products were obtained as single isomers.

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are easy handling and good yields in most cases. No by-products such as amides by amide-ester exchanging were obtained.

By refluxing certain β-dicarbonyl compounds (see Scheme 1) with bromopropylamine, tetrahydropyridine derivatives could be obtained in a one-pot reaction either in the presence (1 equiv.) or absence of acetic acid.

While coupling with an iodocyclization, the synthesis of an indolizidine ring system (see Scheme 2) was also tested, and we could obtain substituted indolizidine compounds in good isolated yield.[21] This protocol might be utilized in the synthesis of indolizidine derivatives that are of interest for medicinal chemistry.

In summary, we have developed an alternative method towards the synthesis of β-enaminones and β-enamino esters. The present method is competitive especially for the synthesis of β-amino-α,β-unsaturated esters that could not be made in good yield by previously reported procedures. This method is easy to perform, efficient, environmentally friendly and most of all it is highly compatible with functional groups presented in the substrates. Its potential for the synthesis of β-amino acid as well as tetrahydropyridine derivatives was also demonstrated.

Experimental

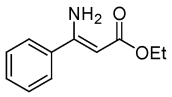
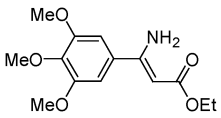
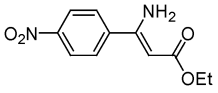
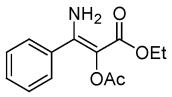
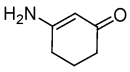
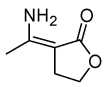
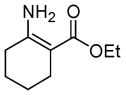
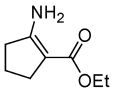
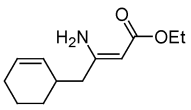
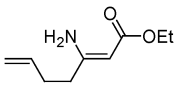
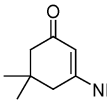
General methods

Proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (^{13}CNMR) was recorded on Bruker Avance 300 spectrometer at 75 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Low resolution mass spectra were recorded on Finnigan Trace 2000 GC-MS spectrometer. Starting materials and reagents used in the reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated.

General procedure

To a solution of 1,3-β-dicarbonyl compounds (1 mmol) and tetraethyl orthosilicate (2 mmol) in absolute ethanol (5 mL),

Table 2 Synthesis of β-enamino esters and β-enaminones[a]

Entry	Product	Yield (%)
1		95
2		94
3		81
4		32
5		98
6		98
7		99[b]
8		90
9		91
10		93
11		94[b]

[a] Reaction was conducted in absolute ethanol with keto esters (1 mmol) and NH_4OAc (4 mmol) in the presence of tetraethyl orthosilicate (2 mmol). The progress of reactions was monitored by TLC. Yields represent isolated yields through chromatography on silica gel or basic Al_2O_3. All products were obtained as single isomers. [b] Products were unstable towards chromatography on silica gel.

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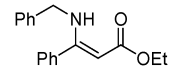
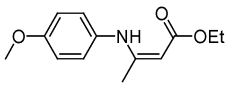
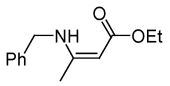
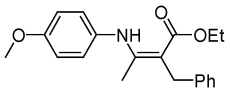
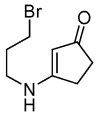
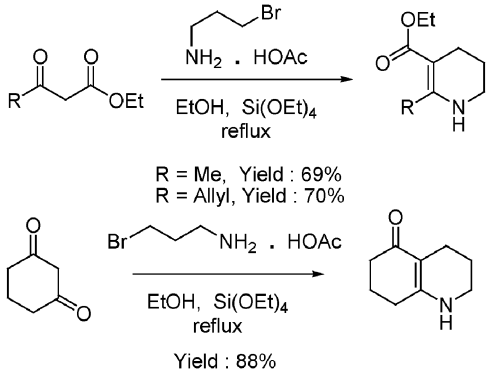
Table 3 Synthesis of β-enamino esters and β-enaminones[a]

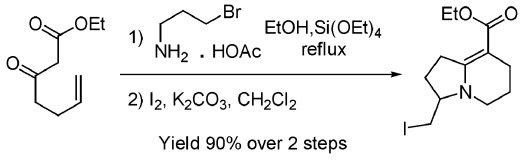
Entry	Product	Yield (%)
1		90
2		92
3		92
4		94
5		99

[a] Reaction was conducted in absolute ethanol with keto esters (1 mmol), primary amine (1.2 mmol) and HOAc (1.2 mmol) in the presence of tetraethyl orthosilicate (2 mmol). The progress of reactions was monitored by TLC. Yields represent isolated yield through chromatography on silica gel or basic Al_2O_3. All products were obtained as single isomers.



Scheme 1 Synthesis of tetrahydropyridine derivatives.

ammonium acetate (4–5 mmol, 4–5 equiv.) or (aryl) alkylammonium acetate (prepared *in situ* from equimolar amounts of aryl or alkylamine and acetic acid, 1.2–1.5 mmol) was added. The resulting mixture was then stirred at reflux under nitrogen for 3–48 hours. The reaction was monitored by thin layer chromatography. After removal of the solvents, the residue



Scheme 2 Synthetic approach towards the indolizidine ring system.

was chromatographed on silica gel or on basic alumina to afford the products.

Acknowledgements

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20 Tetraethyl orthosilicate has dual functions. It serves as a Lewis acid as well as a dehydration agent. In the absence of $Si(OEt)_4$, less than 40% product was formed for the reaction of ethyl benzoylacetate with NH_4OAc in refluxing absolute ethanol (14 hours). In the presence of a catalytic amount of $Si(OEt)_4$ (10% mol), however, the same reaction provided the desired product in 50% yield (14 hours). Complete conversion of ethyl benzoylacetate to the corresponding enaminoester was observed with 2 equiv. of $Si(OEt)_4$ being employed (4 hours). When water (10 mmol) was introduced to the reaction system of ethyl benzoylacetate (1 mmol), NH_4OAc (4 mmol) and $Si(OEt)_4$ (2 mmol) in refluxing absolute ethanol (5 mL), 87% yield was obtained with prolonged reaction times (14 hours). In this case, tetraethyl orthosilicate mainly served as a Lewis acid.

21 Procedure to synthesize the indolizidine derivative: ethyl 3-oxo-hept-6-enoate (1 mmol), bromopropylammonium acetate (1.2 mmol) and tetraethyl orthosilicate (2 mmol, 2.0 equiv.) in absolute ethanol (5 mL) were stirred at reflux. The reaction progress was monitored by thin-layer chromatography. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (5 mL) and iodine (1.2 mmol) and Na_2CO_3 (3 mmol) was added. The resulting mixture was stirred at room temperature for 20 hours. The reaction was monitored by thin-layer chromatography. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 10 mL). The organic phases were combined and washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel to afford the pure products as a pale yellow syrup (90% yield). 3-Iodomethyl-1,2,3,5,6,7-hexahydro-indolizine-8-carboxylic acid ethyl ester: ^{1}HNMR (300 MHz, $CDCl_3$): δ 4.07 (2H, q, J = 7.1 Hz), 3.48–3.34 (1H, m), 3.31 (1H, dd, J = 2.4, 10.4 Hz), 3.23–3.10 (1H, m), 3.18 (1H, dd, J = 6.9, 10.4 Hz), 3.10–2.91 (3H, m), 2.40–2.20 (2H, m), 2.20–1.98 (1H, m), 1.90–1.70 (3H, m), 1.21 (3H, t, J = 7.1 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): δ 168.70, 158.56, 88.99, 63.23, 58.65, 42.97, 30.65, 27.91, 21.60, 21.48, 14.83, 10.44. GC-MS (EI) m/z: 335.1 (M^+, 33%), 306.0 (16), 290.0 (31), 262.0 (10), 208.1 (36), 194.2 (100), 180.1 (21), 166.1 (24), 162.1 (19), 148.1 (42), 134.0 (72), 120.1 (45), 106.1 (15), 91.0 (8).

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