

Short communication

Sc(OTf)₃ catalyzed highly rapid and efficient synthesis of β-enamino compounds under solvent-free conditions

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Received 25 October 2005; received in revised form 22 February 2006; accepted 19 April 2006

Available online 5 June 2006

Abstract

β-Dicarbonyl compounds undergo smooth condensation with aliphatic and aromatic amines in the presence of scandium triflate (Sc(OTf)₃) under solvent-free conditions to afford the corresponding β-enamino compounds in excellent yields. The catalyst can be recovered by simple filtration and can be recycled in subsequent reactions. The method is simple, cost-effective and environmentally benign.

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Keywords: Scandium triflate; β-Keto esters; β-Enaminoesters; Solvent-free condition

1. Introduction

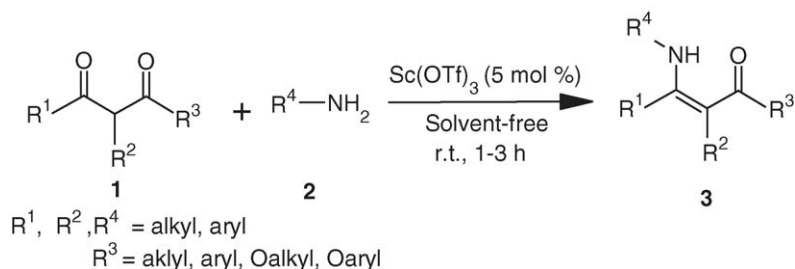
β-Enamino compounds are useful intermediates in pharmaceuticals and as building blocks for the synthesis of a variety of heterocyclic compounds, β-amino esters, β-amino acids, γ-amino alcohols, peptides, and alkaloids [1–7]. Due to the importance of these compounds as intermediates in organic synthesis, a simple a high yielding one-pot approach for this transformation is highly desirable. The most important and straightforward method involves the direct condensation of β-dicarbonyl compounds with amines at reflux in an aromatic solvent with azeotropic removal of water [8]. Also several improved procedures including the reaction of amines and 1,3-dicarbonyl compounds supported on silica with microwave irradiation [9a], clay K-10/ultra-sound [9b], NaAuCl₄·2H₂O [9c], Zn(ClO₄)₂·6H₂O [9d] Bi(TFA)₃ [9e], CeCl₃·7H₂O [9f] have been reported. Recently, these compounds have been prepared by direct condensation of β-dicarbonyl compounds and primary amines in water as a solvent [9g]. However, these methods suffer from one or more drawbacks such as the use of expensive or less readily available reagents, vigorous reaction conditions, longer reaction times, unsatisfactory yields, low selectivity or the use of toxic solvents that limit these methods to small scale

synthesis. Due to the importance of these compounds in organic synthesis, the development of facile and ‘green’ synthetic methods to the β-enaminones under mild reaction conditions is still worthwhile. In recent years, solvent-free reactions have gained popularity as they provide an opportunity to work with an open vessel. This avoids the risk of the development of high internal pressure and provides a possibility of up-scaling the reaction under dry conditions.

Scandium triflate is a new type of Lewis acid that is different from the traditional Lewis acids, such as AlCl₃, BF₃·OEt₂ and SnCl₄, etc. While most of the Lewis acids are deactivated or some times decomposed in the presence of water, Sc(OTf)₃ is stable to water and works as an efficient Lewis acid in aqueous solutions. In addition Sc(OTf)₃ can be recovered via aqueous work-up and can be recycled in subsequent reactions. This produces Sc(OTf)₃ relatively environmentally acceptable as a catalyst in functional group transformations. Therefore over recent years, Scandium triflate has been exploited as a promising and selective reagent for a variety of functional group transformations, especially as a Lewis acid in Aldol condensation reactions, Diels–Alder reactions, Friedel–Crafts reactions, Michael reactions and Fries-rearrangements [10]. However, there is no report of the application of Sc(OTf)₃ as catalyst for the direct one-pot condensation of β-dicarbonyl compounds with amines to produce β-enaminones.

In continuation of our investigation in exploring the use of Sc(OTf)₃ as an efficient catalyst compared to traditional Lewis

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Scheme 1.

acids in several carbon–carbon bond forming reactions [11], we wish to describe $\text{Sc}(\text{OTf})_3$ as an efficient and mild catalyst for the synthesis of *N*-substituted β -enaminones **3** by direct one-pot condensation of β -dicarbonyls **1** with aliphatic and aromatic amines **2** (Scheme 1).

2. Experimental

2.1. General methods

Proton nuclei magnetic resonance (^1H NMR) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and Varian Gemini 200 spectrometer at 200 MHz. Chemical shifts are given in parts per million (ppm) with respect to internal TMS for all recorded NMR spectra, and *J* values are quoted in hertz (Hz). Mass spectra were recorded on VG Micro mass-7070 H spectrometer at 70 eV. IR spectra were recorded on Nicolet-740 FT IR spectrometer. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F₂₅₄). Starting materials and reagents used in the reactions were obtained commercially from Aldrich, Lancaster, Across, Fluka and were used without purification, unless otherwise indicated.

2.2. General procedure

A mixture of β -keto carbonyl (1.0 mmol) and amine (1.0 mmol) was stirred at room temperature in the presence of $\text{Sc}(\text{OTf})_3$ (5 mol.%) for the appropriate time according to Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reac-

tion mixture was extracted with diethyl ether (2 × 10 ml). The catalyst recovered was dried in the oven at 80 °C and reused for three to four times without loss of the activity. The crude products were separated by flash column chromatography on Et₃N pre-treated silica gel using *n*-hexane/EtOAc (10:1) as eluent.

2.2.1. Spectral data for selected products

2.2.1.1. **3a**. 3-Phenylamino-but-2-enoic acid ethyl ester: pale yellow oil; IR (neat): ν_{max} : 2978, 1648, 1620, 1495, 1441, 1270, 1163, 1062, 751, 698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.24 (t, *J* = 7.0 Hz, 3H, CH_3), 2.00 (s, 3H, CH_3), 4.12 (q, *J* = 7.0 Hz, 2H, OCH_2), 4.60 (s, 1H, $\text{H}-\text{C}=\text{C}-$), 7.00–7.10 (m, 3H, ArH), 7.28 (m, 2H, ArH), 10.40 (brs, 1H, NH). EIMS: *m/z* (%): 205 (87) M^+ , 160 (72), 132 (79), 118 (100), 77 (86), 57 (44).

2.2.1.2. **3h**. 4,4,4-Trifluoro-3-phenylamino-but-2-enoic acid ethyl ester: pale yellow oil; IR (neat): ν_{max} : 3468, 2967, 1657, 1606, 1493, 1445, 1363, 1278, 1173, 1032, 777, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.28 (t, *J* = 7.0 Hz, 3H, CH_3), 4.20 (q, *J* = 7.0 Hz, 2H, OCH_2), 5.32 (s, 1H, $\text{H}-\text{C}=\text{C}-$), 7.20–7.30 (m, 3H, ArH), 7.34–7.40 (m, 2H, ArH), 9.90 (brs, 1H, NH). EIMS: *m/z* (%): 260 (90) M^+ , 213 (55), 187 (9), 144 (100), 117 (10), 77 (29), 57 (20).

3. Results and discussion

In a typical general experimental procedure, β -dicarbonyls **1** and an amine **2** was reacted under solvent-free conditions in the presence of a catalytic amount of $\text{Sc}(\text{OTf})_3$ (5 mol%) for a certain period of time required to complete for the reaction. The resulting *N*-substituted β -enaminones **3** was extracted from the reaction mixture and the catalyst recovered was re-used for three to four times without loss of activity, even after fourth cycle the product **3** was obtained with the similar yield and purity of those obtained in the first cycle.

Among the various metal triflates such as $\text{Sc}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, $\text{Bi}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$, and $\text{Zn}(\text{OTf})_2$, used for this reaction in order to compare the catalytic activity in the reaction between ethylacetoacetate **1a** and aniline **2a**, scandium triflate was found to be most effective in terms of conversion and reaction time (Table 1). The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. In the absence of the catalyst the reaction between **1a** and **2a** yielded only 10% of the product **3a** even after 24 h. This reaction carried out with 5, 10, and 20 mol% catalyst load resulted in the reaction yields 95, 95.2 and 95.4%,

Table 1
Condensation of ethylacetoacetate (**1a**) with aniline (**2a**) in presence of various catalysts under solvent-free conditions

Entry	Catalyst (mol.%)	Time (h)	Yield (%) ^a
1	$\text{Yb}(\text{OTf})_3$ (10)	12	77
2	$\text{Y}(\text{OTf})_3$ (10)	12	79
3	$\text{In}(\text{OTf})_3$ (10)	12	82
4	$\text{Bi}(\text{OTf})_3$ (20) ^b	12	75
5	$\text{Cu}(\text{OTf})_2$ (20) ^b	12	70
6	$\text{Zn}(\text{OTf})_2$ (20)	12	70
7	$\text{Sc}(\text{OTf})_3$ (20)	1.0	95.4
8	$\text{Sc}(\text{OTf})_3$ (10)	1.0	95.2
9	$\text{Sc}(\text{OTf})_3$ (5)	1.0	95

^a Isolated and unoptimized yields.

^b Reaction carried at 60 °C.

Table 2
Sc(OTf)₃ catalyzed synthesis of enamino compounds

Entry	1,3-Dicarbonyls	Amine	Product ^a	Time (h)	Yield ^b (%)
1				1.0	95
2				1.5	91
3				2.0	93
4				3.0	89
5				2.5	90
6				2.0	87
7				2.5	89
8				2.5	92
9				3.0	89
10				2.0	87
11				3.0	87
12				3.0	87
13				1.5	85
14				3.0	83
15				2.0	90
16				2.5	84
17				3.0	85
18				2.0	92

^a All products were characterised by ¹H NMR, IR and Mass spectroscopy.

^b Yield refers to pure products after column chromatography.

respectively. Use of just 5 mol% Sc(OTf)₃ is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the yields to greater extent.

To study the generality of this process, several examples illustrating this method for the synthesis of *N*-substituted β -enaminones **3** were studied. This methodology can be applied to various β -dicarbonyls including β -ketoesters, α -substituted 1,3-dicarbonyls, symmetrical and asymmetrical 1,3-diketones, giving in all cases good to excellent yields of β -enaminones with various amines such as primary, secondary, benzylic and aromatic amines. Various β -dicarbonyls **1** and aromatic amines **2** (Table 2, entries 1–11) containing electron-withdrawing groups (such as chloro, fluoro groups, etc.) and electron-donating groups (such as alkyl, hydroxy, methoxy) were employed and they were found to react well to give the corresponding *N*-substituted β -enaminones **3** in good to excellent yields. The effect of electron and the nature of substituents of the aromatic ring did not show strongly obvious effects in terms of yields under this reaction conditions. Aliphatic amines also reacted efficiently to yield the corresponding enaminones in good yields (Table 2, entries 12–17). And also secondary amines reacted smoothly to afford the corresponding enaminones (Table 2, entry 18). This method is equally effective with symmetrical and unsymmetrical 1,3-diketones. In the case of unsymmetrical 1,3-diketones, the regiochemistry is controlled by the more reactive carbonyl group, which undergoes the attack of amine (Table 2, entry 11). Moreover this method is applied to α -substituted 1,3-dicarbonyl compound (Table 2, entry 17) effectively. In all the cases the reactions proceeded smoothly at room temperature. In addition, all these reactions were carried out under solvent-free conditions and the products were characterized by ¹H NMR, ¹³C NMR, Mass and IR spectroscopy. The results are summarized in Table 2.

4. Conclusion

In conclusion, we have described a novel, efficient, convenient and one-pot for the synthesis of *N*-substituted β -enaminones catalyzed by Sc(OTf)₃ under solvent-free conditions. In addition, the attractive features of this procedure are mild reaction conditions, high yields, cleaner reaction profiles, solvent-free conditions, operational simplicity, inexpensive and readily available catalyst which make it a useful and attractive strategy for the preparation of *N*-substituted β -enaminones. Moreover, reusability, stability and non-toxicity of the catalyst are the other noteworthy advantages of this method.

Acknowledgements

V.N.K., R.S.R. thank CSIR New Delhi for the award of fellowships. ICT Communication No. 050902.

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