Synthetic Communications®, 40: 2506–2512, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.493722

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MILD AND EFFICIENT METHOD FOR SYNTHESIS OF EAMINONES USING YTTERBIUM TRIFLATE AS CATALYST

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A mild and efficient procedure for synthesis of β-enaminones by the condensation of β-dicarbonyl compounds and amines using ytterbium triflate [Yb(OTf)$_3$] as catalyst is described. The catalyst can be easily recovered and reused without loss of activity.

Keywords: Amine; β-dicarbonyl compounds; β-enaminones; ytterbium triflate

Enaminones are important precursors for the synthesis of a variety of heterocycles[1] and pharmaceutical compounds.[2] They are known to possess a variety of medicinal properties including anticonvulsant, antimalarial, anti-inflammatory, and cardiovascular effects. Because of the importance of these compounds as intermediates in organic synthesis, several methods for the preparation of β-enaminones have been reported.[2] The conventional method for the synthesis of enaminones is the direct condensation of β-dicarbonyl compounds with amines under reflux in an aromatic solvent with azetropic removal of water.[3] Recently, improved procedures have been reported using all kinds of catalysts such as silica/microwave irradiation,[4] clay K_{10}/ultrasound irradiation,[5] $NaAuAl_4$,[6] $Bi(TFA)_3$,[7] $Zn(ClO_4)_2 \cdot 6H_2O$,[8] $CeCl_3 \cdot 7H_2O$,[9] ionic liquids,[10] and I_2.[11] Nevertheless, some of the approaches currently available suffer from one or more drawbacks such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction times, unsatisfactory yields, or poor selectivity. Taking into consideration of all these limitations and the wide range of activity of enaminones, there is still a need to develop a suitable method for the synthesis of enaminones.

In the past few years, we were interested in the use of metal triflates as Lewis acid promoters in various organic transformations.[12] In the course of our research on metal triflates, we found that they are relatively nontoxic, fairly stable, and efficient catalysts. Herein, we report the use of metal triflates as recyclable catalysts

Received April 13, 2007.

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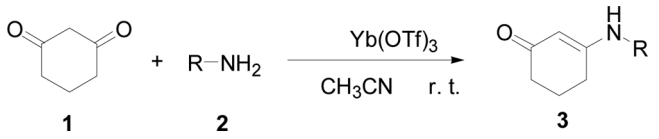


Scheme 1. The synthesis of β-enaminones.

for the synthesis of β-enaminones using cyclohexane-1,3-dione and amine under mild reaction conditions (Scheme 1).

We began our study by comparing the catalytic activity of different metal triflates. Most the catalysts listed in Table 1 were active and stable, and $Yb(OTf)_3$ proved to be the most efficient because the reaction could be carried out in excellent yield. The best reaction conditions require the presence of a small amount of $Yb(OTf)_3$ (2 mol%). In addition, because the $Yb(OTf)_3$ was weakly soluble in CH_2Cl_2 and the products had high solubility in CH_2Cl_2, the products could be extracted with CH_2Cl_2. The catalyst was separated by filtration and dried at 150 °C. The catalyst could be reused for four times without loss of activity (Table 1, entry 13).

The results presented in Table 2 indicated the scope and generality of the method, which is efficient not only for aromatic amines but also for aliphatic amines. The electron-withdrawing group on aromatic amines would draw back the reaction (Table 2, entry 1). The protocol was also successfully applied to enamination of linear β-diketones (Scheme 2; Table 2, entry 11) and linear β-ketoesters (Scheme 2; Table 2, entries 12 and 13). In most cases, the reaction proceeded rapidly and smoothly at room temperature in comparison to other methods, and the products were obtained in excellent yields.

A probable mechanism for the synthesis involving cyclohexane-1,3-dione may be postulated as shown in Scheme 3. First, the amino group attacks the carbomyl

Table 1. Preparation of 3-phenylamino-cyclohex-2-enone (**3e**) under different conditions[a]

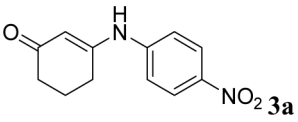
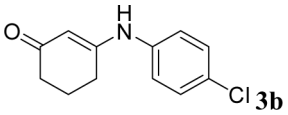
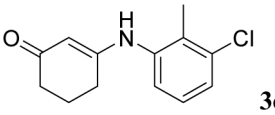
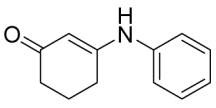
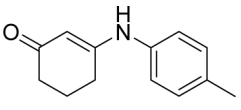
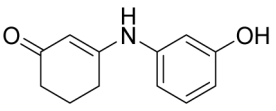
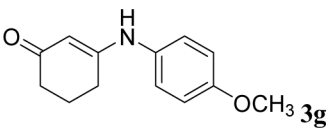
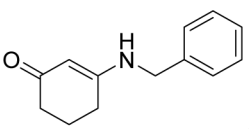
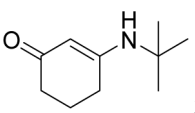
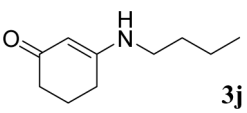
Entry	Catalyst	Cat. amount (mol%)	Yield of **3e** (%)[b]
1	—	—	30
4	$Yb(OTf)_3$	1	70
5	$Yb(OTf)_3$	2	96
6	$Yb(OTf)_3$	3	96
7	$Yb(OTf)_3$	4	96
8	$Yb(OTf)_3$	5	97
9	$Zn(OTf)_2$	2	85
10	$Cu(OTf)_2$	2	93
11	$Eu(OTf)_2$	2	92
12	$Y(OTf)_2$	2	94
13[c]	$Yb(OTf)_3$	2	96, 95, 95, 95

[a]Reaction conditions: cyclohexane-1,3-dione (5 mmol), aniline (5 mmol), CH_3CN as solvent (2 mL), room temperature for 20 min.

[b]Isolated yields.

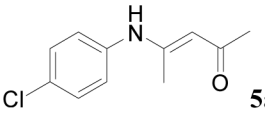
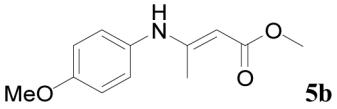
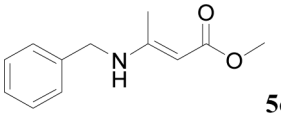
[c]The catalyst was reused for four times.

Table 2. Preparation of β-enaminones catalyzed by $Yb(OTf)_3$[a]

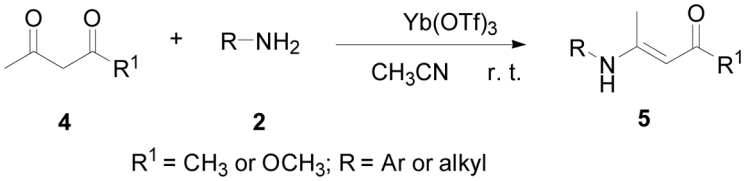
Entry	Reaction time (min)	Products	Yield (%)[c] [Ref.]
1[b]	60	 **3a**	84[14]
2	30	 **3b**	91[4b]
3	30	 **3c**	92[17]
4	20	 **3d**	95[4b]
5	20	 **3e**	96[10]
6	20	 **3f**	94[15]
7	20	 **3g**	97[4b]
8	10	 **3h**	98[2b]
9	10	 **3i**	97[16]
10	10	 **3j**	96[4b]

(*Continued*)

Table 2. Continued

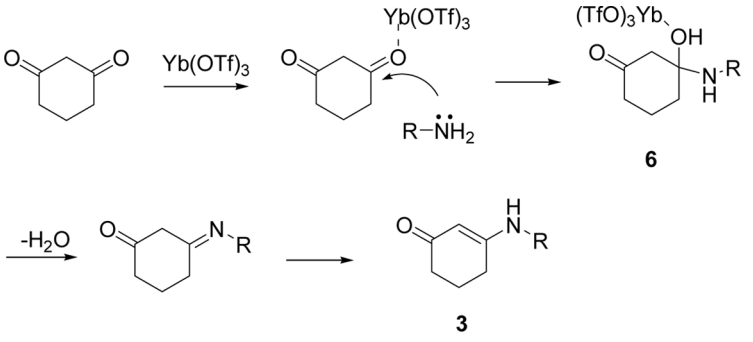
Entry	Reaction time (min)	Products	Yield (%)[c] [Ref.]
11	20	 **5a**	90[4b]
12	20	 **5b**	93[18]
13	20	 **5c**	93[13]

[a]Reaction conditions: β-dicarbonyl compound (5 mmol), amine (5 mmol), $Yb(OTf)_3$ (0.10 mmol), CH_3CN as solent (2 mL), room temperature.
[b]Reaction temperature: 60 °C.
[c]Isolated yields.



4 **2** **5**

Scheme 2. The direct condensation of cyclohexane-1,3-dione and amine catalyzed by ytterbium triflate.



6 **3**

Scheme 3. Proposed mechanism for the condensation reaction of cyclohexane-1,3-dione and amine.

group of cyclohexane-1,3-dione, which is activated by $Yb(OTf)_3$, giving the intermediate **6**, which was intramolecular dehydrated to give the corresponding product **3**.

In conclusion, we have developed a novel and efficient method for the synthesis of β-enaminones by treating β-dicarbonyl compounds with amines in the presence of $Yb(OTf)_3$. The mildness of the conversion, simple experimental procedure, good yields, short reaction times, and reusability of the catalyst are the noteworthy advantages of the protocol.

EXPERIMENTAL

All reagents were used as received. ^1H NMR spectra were recorded on a Varian 400-MHz instrument using dimethylsulfoxide (DMSO) as the solvent. Chemical shifts were expressed in parts per million using tetramethylsilane (TMS) as an internal standard.

General Procedure for the Preparation of β-Enaminones

A mixture of the β-dicarbonyl compounds (5 mmol), amine **2** (5 mmol), and $Yb(OTf)_3$ (0.10 mmol, 0.062 g) in acetonitrile (2 mL) was stirred at room temperature (or 60 °C; Table 2, entry 1) for the appropriate time (Table 2). After completion of the reaction as indicated by thin-layer chromatography (TLC), the mixture was diluted by CH_2Cl_2 (20 mL). The insoluble catalyst was separated by filtration and rinsed with CH_2Cl_2. Then it was dried at 150 °C for 2 h to give a white solid, which could be reused without loss of activity. The organic liquid was concentrated under reduced pressure and then recrystallized from petroleum ester and ethyl acetate (V/V = 3:1) to give pure products **3**.

Spectral Data of Selected Compounds

3-(4-Nitrophenylamino)cyclohex-2-enone 3a. ^1H NMR (400 MHz, DMSO): δ 9.34 (s, 1 H, NH), 8.22 (d, $J = 8.8$ Hz, 2H, ArH), 7.38 (d, $J = 8.8$ Hz, 2 H, ArH), 5.69 (s, 1 H, CH=C), 2.58 (t, $J = 6.0$ Hz, 2 H, CH_2), 2.26 (t, $J = 6.4$ Hz, 2 H, CH_2), 1.94 (q, $J = 6.0$ Hz, 2 H, CH_2). ^{13}C NMR (100 MHz, DMSO): 196.7, 159.4, 146.2, 141.6, 125.2 120.3, 102.4, 36.4, 28.6, 21.3.

3-(3-Chloro-2-methylphenylamino)cyclohex-2-enone 3c. ^1H NMR (400 MHz, DMSO): δ 8.71 (s, 1 H, NH), 7.38 (d, $J = 8.4$ Hz, 1 H, ArH), 7.26 (t, $J = 8.0$ Hz, 1 H, ArH), 7.15 (d, $J = 8.0$ Hz, 1 H, ArH), 4.58 (s, 1 H, CH=C), 2.53 (t, $J = 6.0$ Hz, 2 H, CH_2), 2.20 (s, 3 H, CH_3), 2.15 (t, $J = 6.0$ Hz, 2 H, CH_2), 1.90 (q, $J = 6.0$ Hz, 2 H, CH_2). ^{13}C NMR (100 MHz, DMSO): 195.3, 163.7, 138.6, 134.4, 132.4, 127.5, 127.2, 126.0, 97.8, 36.4, 27.9, 21.6, 14.9.

3-(p-Toluidino)cyclohex-2-enone 3e. ^1H NMR (400 MHz, DMSO): δ 8.79 (s, 1 H, NH), 7.17 (d, $J = 8.0$ Hz, 2 H, ArH), 7.06 (d, $J = 8.4$ Hz, 2 H, ArH), 5.26 (s, 1 H, CH=C), 2.49 (t, $J = 6.0$ Hz, 2 H, CH_2), 2.28 (s, 3H, CH_3), 2.15 (t, $J = 6.4$ Hz, 2H, CH_2), 1.87 (q, $J = 6.0$ Hz, 2 H, CH_2). ^{13}C NMR (100 MHz, DMSO): 195.6, 162.3, 136.4, 133.7, 129.6, 123.2, 97.6, 36.4, 28.5, 21.6, 20.5.

3-(4-Methoxyphenylamino)cyclohex-2-enone 3g. ^{1}H NMR (400 MHz, DMSO): δ 8.69 (s, 1 H, NH), 7.10 (d, $J = 8.8$ Hz, 2 H, ArH), 6.95 (d, $J = 8.8$ Hz, 2 H, ArH), 5.11 (s, 1 H, CH=C), 3.75 (s, 3 H, OCH_3), 2.47 (t, $J = 6.0$ Hz, 2 H, CH_2), 2.14 (t, $J = 6.4$ Hz, 2 H, CH_2), 1.87 (q, $J = 6.4$ Hz, 2 H, CH_2). ^{13}C NMR (100 MHz, DMSO): 195.3, 163.0, 156.4, 131.6, 125.3, 114.4, 97.0, 55.2, 36.4, 28.4, 21.6.

3-(Benzylamino)cyclohex-2-enone 3h. ^{1}H NMR (400 MHz, DMSO): δ 7.54 (t, $J = 5.2$ Hz, 1 H, NH), 7.36–7.24 (m, 5 H, ArH), 4.80 (s, 1 H, CH=C), 4.20 (d, $J = 6.0$ Hz, 2 H, CH_2), 2.38 (t, $J = 6.4$ Hz, 2 H, CH_2), 2.06 (t, $J = 6.4$ Hz, 2 H, CH_2), 1.79 (q, $J = 6.4$ Hz, 2 H, CH_2). ^{13}C NMR (100 MHz, DMSO): 194.5, 164.4, 138.1, 128.4, 127.3, 127.0, 95.6, 45.6, 36.5, 28.4, 21.7.

3-(*tert*-Butylamino)cyclohex-2-enone 3i. ^{1}H NMR (400 MHz, DMSO): δ 7.18 (brs, 1 H, NH), 4.71 (s, 1 H, CH=C), 2.06–1.96 (m, 4 H, $2 \times CH_2$), 1.73 (q, $J = 6.4$ Hz, 2 H, CH_2), 1.20 (s, 9 H, $3 \times CH_3$). ^{13}C NMR (100 MHz, DMSO): 191.1, 101.6, 49.6, 34.9, 28.5, 21.7.

ACKNOWLEDGMENTS

We are grateful to the National Basic Research Program (No. 2003CB114402) and the National Natural Science Foundation of China (Nos. 20476098 and 20676123) for financial support.

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