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Ytterbium triflate catalyzed synthesis of β-enaminones

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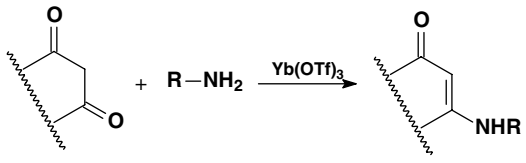
Abstract—β-Enaminones have been synthesized in very good yield under solvent-free conditions from differently substituted amines and β-diketones in the presence of $Yb(OTf)_3$ as catalyst. The method is applicable to cyclic and acyclic ketones, aromatic and aliphatic amines without differences.

β-Enaminones have been extensively used as key intermediates in organic synthesis.[1] In particular they have been employed as synthons of a wide variety of heterocycles[2] and pharmaceutical compounds having anti-epileptic,[3] molluscicidal and larvicidal activities[4] and as intermediates for the synthesis of naturally occurring alkaloids.[5] Despite the importance of β-enaminones as valuable biologically active compounds, their synthesis has received to date little attention. The most well-known and exploited route to β-enaminones involves the direct condensation of β-dicarbonyl compounds with amines in refluxing aromatic hydrocarbons with azeotropic removal of water.[6] Other improved procedures have been subsequently reported and include the reaction of amines with β-dicarbonyl compounds supported on silica under microwave irradiation,[7] montmorillonite K-10 and ultrasounds,[8] the reaction catalyzed by $NaAuCl_4$,[9] bismuth(III) trifluoroacetate,[10] erbium triflate[11] or zirconium(IV) chloride,[12] cyclization of aminoacids,[13] reductive cleavage of silylisoxazoles,[14] the direct condensation of primary amines and β-diketones in water.[15] A detailed survey of all methods for the synthesis of the title compounds have been recently reported.[12] Unfortunately many of these processes suffer major or minor limitations such as drastic reaction conditions, low yields, tedious work-up procedures, low selectivity, co-occurrence of several side reactions and need of chromatography for purification of adducts. Moreover, in the case of some of the Lewis acid catalyzed reactions, no recycling of the catalyst renders these methods environmentally unsound, especially with regard to a potential large-scale synthesis. So although different methods are available for the synthesis of β-enaminones, development of another facile, high-yielding, nonpolluting preparation is still of great importance.

During the last 15 years, rare earth metal triflates have been found as unique Lewis acids in that they are water tolerant reusable catalysts and they can effectively promote several carbon–carbon and carbon–heteroatom bond formation reactions in high yield.[16] As a part of our ongoing studies aimed to explore the utility of lanthanide triflate catalyzed reactions under solvent-free conditions,[17] we decided to investigate the use of $Yb(OTf)_3$ as a catalyst for the preparation of β-enaminones using some reaction conditions recently reported for the synthesis of β-keto enol ethers (Scheme 1).[17] Although Jenner reported in 1996 a procedure aimed to obtain the title compounds under the catalysis of $Yb(OTf)_3$,[18] results reported in this work is mainly focused on the use of secondary amines as starting materials, while results employing primary amines are not reported or gave no desired product or not satisfactory yields, with the only exception of using 2,4-pentanedione



Scheme 1.

Keywords: Amine; β-Enaminone; β-Dicarbonyl compounds; Heterogeneous catalysis; Ytterbium triflate.
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Table 1. $Yb(OTf)_3$ catalyzed formation of β-enaminones

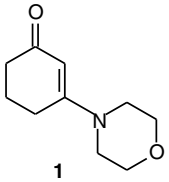
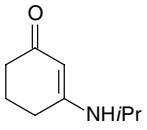
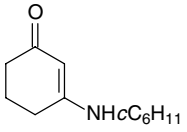
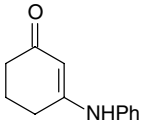
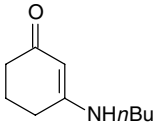
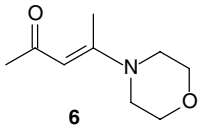
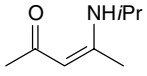
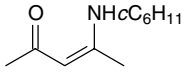
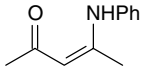
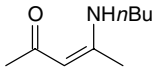
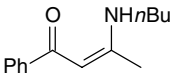
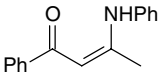
Reactant	Amine	Product	Yield[a] (%)
1,3-Cyclohexanedione	Morpholine	 **1**	99
1,3-Cyclohexanedione	Isopropyl amine	 **2**	97
1,3-Cyclohexanedione	Cyclohexyl amine	 **3**	93
1,3-Cyclohexanedione	Aniline	 **4**	99
1,3-Cyclohexanedione	*n*-Butyl amine	 **5**	99
Acetylacetone	Morpholine	 **6**	99
Acetylacetone	Isopropyl amine	 **7**	98
Acetylacetone	Cyclohexyl amine	 **8**	99
Acetylacetone	Aniline	 **9**	99
Acetylacetone	*n*-Butyl amine	 **10**	99

Table 1 (*continued*)

Reactant	Amine	Product	Yield[a] (%)
Benzoylacetone	*n*-Butyl amine	 **11**	98
Benzoylacetone	Aniline	 **12**	99

[a] Yields of pure isolated products, characterized by IR, GC–MS, ^{1}H NMR and ^{13}C NMR.

as substrate. In addition better yields were obtained only by application of a high-pressure procedure (300 MPa) and carrying out reactions in a toxic and polluting solvent such as chloroform.

We initially tested this type of reaction using cyclic β-diketones as starting materials. The reaction was carried out in neat at room temperature for 12 h using commercially available 1,3-cyclohexanedione (2.0 mmol) and amine (2.0 mmol) in the presence of $Yb(OTf)_3$ hydrate (0.01 mmol) as catalyst. After addition of NaOH 1 N to precipitate Yb(III) as the corresponding hydroxide, the desired product was obtained after filtration and extraction with Et_2O (3×2 mL). Results are summarized in Table 1 and show that primary and secondary amines, aromatic and aliphatic with linear, branched or cyclic N-substituents, react without any significative difference to give the corresponding β-enaminones in good to nearly quantitative yield. Uncatalyzed reactions, carried out in solvent-free conditions, gave in all cases the desired product, after the same time, in yields ranging from 40% to 55%. Loading of the catalyst higher than 0.01 mmol did not decrease reaction times significantly. The degree of purity of each product was analyzed by GC/MS spectrometry, using a Hewlett Packard 6890 gas chromatograph equipped with a 12.5 m × 0.25 mm MetSil column coupled to HP ChemStation Software. The carrier gas was helium at a pressure of 3.5 kg/cm^2 and the column temperature was programmed from 50 to 270 °C at 10 °C/min. The chromatogram was obtained using a reporting integrator. Mass spectra were obtained from a GC–MS system, operating in the EI mode at 70 eV, equipped with a 12.5 m × 0.25 mm MetSil column and an HP 5973 Mass Selective Detector, using the same chromatographic conditions reported above. The column was connected to the mass spectrometer ion source via an open split interface heated at 250 °C.

Employing linear β-diketones as substrates, such commercially available acetylacetone, using the same reaction conditions as above, the corresponding β-enaminones were obtained in very good yield. From linear β-diketones we also obtained the corresponding β-enaminones having a (*Z*) configuration of the carbon–carbon double bond, as determined by ^{1}H NMR analysis and NOE experiments, except in the case of using morpholine as starting amine to give compound **6** where a (*E*) geometry was obtained. The (*Z*) configuration may be thermodynamically favoured by the formation of an intramolecular hydrogen bond formation between oxygen atom of the carbonyl and the NH residue yielding a six-member pseudocycle, while the driving force in determining the geometry of the double bond in compound **6** is the sterically more bulky morpholine ring to assume a trans position with respect to the carbonyl group. Finally we employed also β-diketones with two different substituents, such as the commercially available benzoylacetone. In all cases we obtained selectively the adduct deriving from a nucleophilic attack of the amine to the carbonyl bearing a methyl group.[19] In contrast to data reported by Jenner,[18] our methodology is of general applicability, leading in very good yield to the desired product starting from differently substituted β-diketones and primary or secondary amines.

From every reaction the catalyst have been recovered by precipitation as $Yb(OH)_3$, filtration and transformation into triflate salt as already described.[13] Recycled in this way, the catalyst could be reused several times without any loss of activity.

In conclusion we disclosed an easy environmentally sound method for the synthesis of β-enaminones starting from differently substituted 1,3-diketones and amines under the catalysis of $Yb(OTf)_3$. The simple work-up procedure, mild reaction conditions and high yields make our methodology a valid contribution to the existing processes in the field of β-enaminones synthesis. Further investigations into the scope and other applications of $Yb(OTf)_3$ promoted reactions are now in progress in our laboratories and will be reported in due course.

Synthesis of β-enaminones. A typical procedure: A mixture of β-diketone (2.0 mmol) and amine (2.0 mmol) was well stirred with $Yb(OTf)_3$ (0.01 mmol) at room temperature for 12 h. NaOH 1 N (2 mL) was added, the white precipitate filtered and the resulting solution extracted with Et_2O (3×2 mL). Collected organic phases were dried over anhydrous Na_2SO_4 and the

solvent evaporated to dryness to give the desired β-enaminone in a pure form.

3-Morpholin-4-ylcyclohex-2-en-1-one (**1**): yellow solid (mp: 93–95 °C, lit.[20] 92–94 °C); ^{1}H NMR;[21] ^{13}C NMR;[22] GC/MS: $M^+ = 181$.

3-(Isopropylamino)cyclohex-2-en-1-one (**2**): yellow oil; ^{1}H NMR δ 1.21 (d, 6H, $J = 6.4$ Hz), 1.90–2.03 (m, 2H), 2.29–2.35 (m, 4H), 3.60 (sept, 1H, $J = 6.4$ Hz), 5.13 (s, 1H); ^{13}C NMR δ 21.8, 22.4, 29.2, 36.4, 44.0, 95.8, 164.0, 197.1; GC/MS: M^+ 153.

3-(Cyclohexylamino)cyclohex-2-en-1-one (**3**): pale yellow solid (mp: 147–148 °C); ^{1}H NMR;[23] ^{13}C NMR;[23] GC/MS: $M^+ = 193$.

3-Anilinocyclohex-2-en-1-one (**4**): pale yellow solid (mp: 179–180 °C, lit.[24] 178–180 °C); ^{1}H NMR;[24] ^{13}C NMR;[24] GC/MS: $M^+ = 187$.

3-(Butylamino)cyclohex-2-en-1-one (**5**): pale yellow oil; ^{1}H NMR;[24] ^{13}C NMR;[24] GC/MS: $M^+ = 167$.

(3*E*)-4-Morpholin-4-yl-pent-3-en-2-one (**6**): pale yellow oil. ^{1}H NMR;[9] ^{13}C NMR;[9] GC/MS: $M^+ = 169$.

(3*Z*)-4-(Isopropylamino)pent-3-en-2-one (**7**): pale yellow oil. ^{1}H NMR;[25] ^{13}C NMR;[26] GC/MS: $M^+ = 141$.

(3*Z*)-4-(Cyclohexylamino)pent-3-en-2-one (**8**): orange oil; ^{1}H NMR;[27] ^{13}C NMR;[27] GC/MS: $M^+ = 181$.

(3*Z*)-4-Anilinopent-3-en-2-one (**9**): orange solid (mp: 45–47 °C, lit.[28] 49–50 °C); ^{1}H NMR;[27] ^{13}C NMR;[27] GC/MS: $M^+ = 175$.

(3*Z*)-4-(Butylamino)pent-3-en-2-one (**10**): pale yellow oil. ^{1}H NMR;[24] ^{13}C NMR;[24] GC/MS: $M^+ = 155$.

(2*Z*)-3-(Butylamino)-1-phenylbut-2-en-1-one (**11**): pale yellow oil; ^{1}H NMR;[29] ^{13}C NMR;[30] GC/MS: $M^+ = 217$.

(2*Z*)-3-Anilino-1-phenylbut-2-en-1-one (**12**): orange solid. (mp: 108–109 °C, lit.[28] 109–110 °C); ^{1}H NMR;[31] ^{13}C NMR;[31] GC/MS: $M^+ = 237$.

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