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Vanadium(IV) acetylacetonate catalyzed stereoselective synthesis of β-enaminoesters and β-enaminones

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This work is dedicated to Professor Mihir K. Chaudhuri, Vice-chancellor, Tezpur University on the occasion of his 65th birthday.

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ABSTRACT

An efficient and stereoselective procedure has been described for the synthesis of a series of β-enaminoesters and β-enaminones by vanadium(IV) acetylacetonate [$VO(acac)_2$] catalyzed reaction of β-ketoesters and 1,3-diketones with both aliphatic and aromatic amines. X-ray crystallographic studies of some representative compounds corroborate two types of structural geometry formed by inter-molecular as well as intra-molecular hydrogen bonds.

β-Enaminoesters and β-enaminones are the building blocks for an important class of molecules synthesized from the β-dicarbonyl compounds.[1–4] They are the precursors for a variety of versatile biologically active molecules like taxol, peptides, and alkaloids.[1–8] Chiral ligands for diastereoselective synthesis can also be obtained from the optically active enaminones.[9] Moreover, the β-enaminoesters and β-enaminones are significant intermediates for the formation of β-aminoacids and γ-aminoalcohols. The major advantage of these compounds is their stability under simulated physiological pH conditions and low toxicity.[10] Numerous methods for their syntheses are reported in the literature.[1,11–14] The classical among them, is the condensation of amines and 1,3-dicarbonyl compounds where water is removed azeotropically by refluxing in aromatic solvents. Conversion with catalysts like Al_2O_3,[2] SiO_2,[15] montmorillonite K-10,[16] $NaAuCl_4$,[17] $Zn(ClO_4)_2{\cdot}6H_2O$,[18] AcOH under ultrasound,[19] $Zn(OAc)_2{\cdot}2H_2O$,[20] $Bi(OTf)_3$,[21] I_2,[22] $Sc(OTf)_3$,[23a] $HClO_4{\cdot}SiO_2$,[23b] ionic liquid $[EtNH_3]NO_3$[24] and $[Hmin]^+Tfa^-$,[25] $CeCl_3{\cdot}7H_2O$[26] and $ZrOCl_2{\cdot}8H_2O$,[27a] $H_2SO_4{\cdot}SiO_2$,[27b] ceric ammonium nitrate (CAN),[27c] $LiHSO_4/SiO_2$,[27d] and L-proline[27e] have also been reported recently. In spite of their applicability, these methods suffer from drawbacks like prolonged reaction time,[2,15] high temperature,[19] formation of amides as side products, expensive catalysts,[12,17,21] high catalyst loading,[20,22,26] and the use of hazardous solvents for example, benzene. Thus, a search for a new catalyst and simple procedure is of practical importance.

Vanadium acetylacetonate [$VO(acac)_2$] has been proven as a remarkable reagent in various organic syntheses due to its wide spectrum of applicability and profound reactivity. This low cost reagent is convenient to handle due to extremely low toxicity.[28a] Moreover, it is soluble in organic solvents. The catalytic activity of $VO(acac)_2$ in the epoxidation of alkenes and geraniol, oxidation of dialkyl disulfides, and selective aerobic oxidation of activated alcohols into acids or aldehydes is well-known in the literature.[28–30] Recently, the use of $VO(acac)_2$ as catalyst has been reported in the oxidation of β-dicarbonyl compounds,[31] olefination of α,α′-divinyl ketones through catalytic Meyer–Schuster rearrangement,[32a] synthesis of benzimidazoles,[32b] and synthesis of carbon nanospheres.[33] Very recently, we have demonstrated that a combination of $VO(acac)_2$, hydrogen peroxide, and sodium iodide is a good system for cleavage of dithioacetals of sugars into aldehyde sugars[34a] and iodination of various organic substrates.[34b] To

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the best of our knowledge, $VO(acac)_2$ catalyzed synthesis of β-enaminoesters and β-enaminones from β-ketoesters and 1,3-diketones has not yet been reported. Herein, we report an easy and selective procedure for the synthesis of a series of β-enaminoesters and β-enaminones from β-ketoesters and 1,3-diketones respectively using 10 mol % of $VO(acac)_2$ as catalyst as shown in Scheme 1.

For our study, the catalyst $VO(acac)_2$ was prepared by following the literature procedure.[35] For optimization of the reaction conditions, a mixture of methyl acetoacetate (2.4 mmol) and benzyl amine (2.0 mmol) was stirred at room temperature without adding any catalyst. After 3 days of continuous stirring, the desired product **3a** was obtained in 55% yield along with unreacted starting materials. Next, the same mixture was stirred at room temperature in the presence of 1 mol % of vanadyl acetylacetonate and the product **3a** was isolated in 65% yield (Table 1, entry 2). Likewise, similar reactions were examined with 2 mol %, 5 mol %, 10 mol %, and 15 mol % successively and we have noted that 10 mol % catalyst is a sufficient amount for complete conversion as well as to obtain the best yield (Table 1, entries 3–6). However, the same transformation can be achieved using 5 mol % catalyst, but it requires longer duration. The product 3a was characterized by recording ^1H NMR, ^{13}C NMR spectra, and elemental analysis.

After optimizing the reaction conditions,[36] the reaction of a wide variety of β-ketoesters (**1b–j**) was examined with benzyl amine using 10 mol % of $VO(acac)_2$ at room temperature and the desired products **3b–j** were obtained in good yields (Table 2, entries **b–j**). Similarly, various β-ketoesters (**1k–s**) and aromatic amines were scrutinized in the presence of 10 mol % catalyst under identical reaction conditions and the products (**3k–s**) were isolated in moderate to good yields. It is worth-while to mention that electron-rich aromatic amines take a shorter reaction time and provide good yields as compared to aromatic amine having electron-withdrawing substituents. Encouraged by these results, various 1,3-diketones (**1t–x**) were treated with different aromatic amines and benzyl amine using the same amount of catalyst under similar reaction conditions and the results are given in Table 2.

Interestingly, acyclic β-ketoesters and 1,3-diketones result *Z*-β-enaminoesters and *Z*-β-enaminones with 100% stereoselectivity, respectively, whereas cyclic 1,3-diketones give exclusively *E*-β-enaminones as shown in Scheme 1.

From Table 2, it can be seen that the nucleophilic benzylamine reacts faster with a variety of β-ketoesters and 1,3-diketones to give β-enaminoesters and β-enaminones in excellent yields as compared to 2-methoxyaniline (entry **1l**) and 2,6-dimethylaniline (entry **1o**). A plausible mechanistic pathway has been outlined in Scheme 2.

To shed further light on the geometry of the compounds, the molecular structures of **3t** and **3v** were confirmed by a single crystal X-ray analysis (Fig. 1).[37] X-ray crystallographic experiments

Table 1
Optimization of reaction condition using $VO(acac)_2$ catalyst[a]

Entry	Catalyst used	Catalyst amount in (mol %)	Reaction time (min)	Product	Yield[b] (%)
1	No Catalyst	—	3 days	**3a**	55
2	$VO(acac)_2$	1	90	**3a**	65
3	$VO(acac)_2$	2	50	**3a**	74
4	$VO(acac)_2$	5	30	**3a**	90
5	$VO(acac)_2$	10	15	**3a**	93
6	$VO(acac)_2$	15	15	**3a**	92

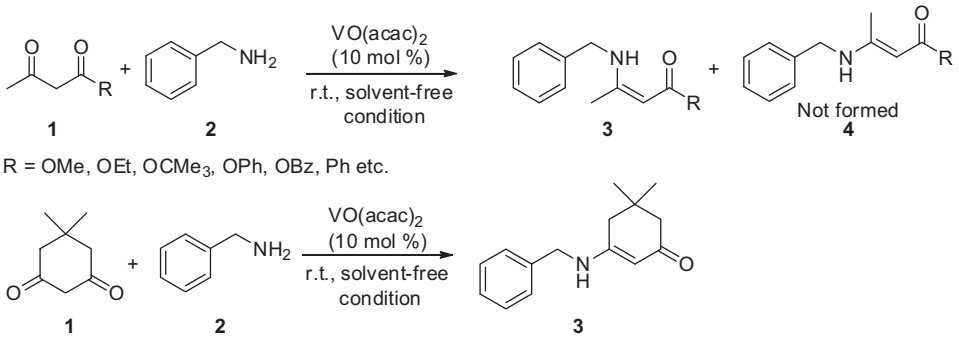
[a] The reactions were carried out with methyl acetoacetate (2.4 mmol) and benzyl amine (2.0 mmol).
[b] Isolated yield.

reveal that **3t** belongs to the triclinic space group $P\bar{1}$ with $Z = 4$ whereas **3v** belongs to the monoclinic space group $P2_1/n$ with $Z = 4$. Crystal structure analysis shows that **3t** forms two independent discrete molecules because of intra-molecular hydrogen bonding interactions (O···H = 1.93 Å, O···N = 2.696 Å and O···H = 1.74 Å, O···N = 2.698 Å) leading to the formation of quasi-aromatic ring. On the other hand, **3v** forms 1D polymer via intermolecular hydrogen bonding interactions through C═O···H–N bonds (O···H = 1.99 Å, O···N = 2.810 Å, ∠O···H–N = 159°). The hydrogen-bonded ring formation could not be possible in the case of **3v** due to the structural constraint as shown in Figure 1a.

The ^1H NMR spectra of the products show two different kinds of chemical shifts of NH protons. Notably, the NH proton of β-enaminone (entry **3v** and **3w**) (derived from dimedone and benzylamine or dimedone and *p*-ethyl aniline) was found at 4.80 ppm and 5.95 ppm which supports the formation of *E*-isomer. In this case the intermolecular hydrogen bond causes the compound to become a 1D-zigzag hydrogen-bonded polymeric form as evident from the X-ray crystallographic structure of Figure 1a. The downfield shift of the NH proton is in the range of δ value 8.9–12.5 ppm which indicates the predominant formation of the *Z*-β-enaminoesters or *Z*-β-enaminones. The intra-molecular hydrogen bonding plays the key role in maintaining the geometry of the molecule intact and responsible for higher δ values because of the formation of quasi-aromatic ring which is evident from Figure 1b.

Again in the case of unsymmetrical diketone, benzoyl acetone (entries **3t–u**), the amine always attacked the keto group positioned α- to the methyl group and in all cases; this is evident from the ^1H NMR spectra. The methyl group exhibited a distinctive singlet at 2.07 ppm, instead of 2.22 ppm which is a characteristic peak of the methyl group of $-COCH_3$.

Stereoselective syntheses of enaminones and enaminoesters using various catalysts have been well-studied.[21,23b,27c] However, it provides further scope to design a particular substrate to obtain stereoselective products unequivocally. The major advantage of our procedure is the stereoselective formation of the products owing to the intermolecular and intramolecular hydrogen-bonding.



Scheme 1.