



VB₁–Al₂O₃-catalyzed one-pot condensation of aromatic ketone, aromatic aldehyde, and amide

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ABSTRACT

A novel and green approach for the efficient synthesis of β -amido ketones using VB₁–Al₂O₃ as a heterogeneous catalyst for the first time from an aldehyde, enolizable ketones, and an amide in EtOH is described. The present methodology has several advantages from the economical and environmental points of view, such as simple procedure, low catalyst loading, high atom economy, and good yields.

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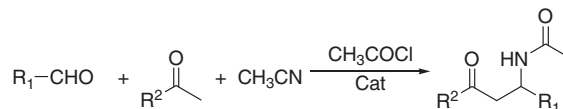
Carrying out an organic reaction using solid-supported catalysts has become highly desirable in recent years to meet the environmental considerations.¹ The common features of solid-supported catalysts are low toxicity, moisture resistance, air tolerance, and low price. The literature conveys that they can effectively promote several carbon–carbon and carbon–heteroatom bond formation reactions in good yields.²

β -Amido ketones are important intermediates in organic synthesis due to their multifunctional nature and presence in several bioactive compounds.³ They can be converted into amino alcohols,⁴ β -amino acids,⁵ and γ -lactams,⁶ which may be applied for the synthesis of various important antibiotics.^{4–7} The preparation of β -amido ketones can be carried out by the condensation of aldehydes, enolizable ketones, acetyl chloride, and acetonitrile (Scheme 1) in the presence of Lewis or Brønsted acid catalysts, such as iodine,⁸ montmorillonite K10 clay,⁹ CoCl₂,^{5,10} ZrOC₁₂·8H₂O,¹¹ CeCl₃·7H₂O,¹² Sc(OTf)₃,¹³ heteropoly acid,¹⁴ Nafion-H,¹⁵ FeCl₃·6H₂O,¹⁶ SiCl₄–ZnCl₂,¹⁷ Zr(HSO₄)₄, and Mg(HSO₄)₂.¹⁸ However, this method so far suffers from a low atom economy because the use of stoichiometric amounts of acetyl chloride as an additional reagent is necessary to obtain satisfactory results. Therefore, it is necessary to develop an efficient and versatile method for the synthesis of these compounds.¹⁹

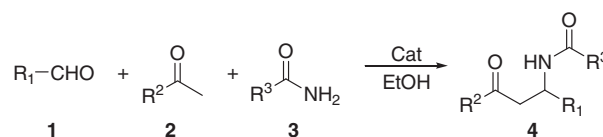
In continuation of our work on the application of heterogeneous catalysts for the development of useful synthetic methodologies, we now show that β -amido ketones can be produced using VB₁–Al₂O₃ as an efficient heterogeneous catalyst via a direct condensation of aldehydes, enolizable ketones, and amides (Scheme 2). To the best of our knowledge, there has been no report on the use of VB₁–Al₂O₃ as a catalyst in synthetic organic chemistry.²⁰

Initially, we investigated the condensation reaction of benzaldehyde **1a** (5 mmol), acetophenone **2a** (5 mmol), and benzamide **3a** (5 mmol) in alcohol (3 mL) as the solvent in the presence of different catalysts and the results are summarized in Table 1.

In this three-component reaction, we found catalysts had significant effects on the reaction time and yields (Table 1). The results indicated that this three-component reaction could not take place in the presence of 10 mol % classical Lewis acid as catalysts, such as ZnCl₂, CuCl₂, MgCl₂, FeCl₃, Yb(OTf)₃, and Cu(ClO₄)₂ (Table 1, entries 1–6). Then, we carried out the reaction using VB₁ as an organocatalyst, but the desired product was not afforded (Table 1, entry 7). Moreover, we also found that this reaction could be carried out in the presence of Al₂O₃ as the catalyst, but the yield was very low (30%). To detect whether the use of VB₁–Al₂O₃ was efficient, we carried out the reaction in EtOH in the presence of 10 mol % VB₁–Al₂O₃ for 15 h to afford the desired product **4a** in 84% yield. Encouraged by the result, we subsequently changed the amount of VB₁–Al₂O₃ from 1 to 10 mol %, finding that 5 mol % had a



Scheme 1. The classical method for the synthesis of β -amido ketones.



Scheme 2. One-pot synthesis of β -amido ketones **4**.

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Table 1
Optimization of catalysts^a

Entry	Catalyst	Catalyst (mol %)	Time (h)	Yield of 4a ^b (%)
1	ZnCl ₂	10	24	0
2	CuCl ₂	10	24	0
3	FeCl ₃	10	24	0
4	MgCl ₂	10	24	0
5	Yb(OTf) ₃	10	24	0
6	Cu(ClO ₄) ₂	10	24	0
7	VB ₁	10	24	0
8	Al ₂ O ₃	0.8 g	24	30
9	VB ₁ -Al ₂ O ₃	10	15	84
10	VB ₁ -Al ₂ O ₃	1	24	50
11	VB ₁ -Al ₂ O ₃	3	18	75
12	VB ₁ -Al ₂ O ₃	5	15	82
13	VB ₁ -Al ₂ O ₃	8	15	82

^a The reaction carried out in EtOH at reflux temperature.^b Isolated yields.

significant improvement in the yield (82%). The results indicated that 5 mol % of VB₁-Al₂O₃ was sufficient and excessive amount of the catalyst did not increase the yields significantly.

In order to find the optimum solvent, the reaction using 5 mol % VB₁-Al₂O₃ as the catalyst was performed in various solvents, such as EtOH, THF, acetonitrile, DMF, DMSO, 1,4-dioxane, CCl₄, and H₂O. Acetonitrile, DMF, and DMSO afforded low yields (22–30%), whereas, when CCl₄, and H₂O were used as solvents, no desired products were detected (Table 2, entries 7 and 8). The reaction using EtOH as the solvent gave the best result (Table 2, entry 1), hence, it was chosen as the solvent for all further reactions.

Furthermore, the recyclable character of VB₁-Al₂O₃ was also investigated. Of particular note was the fact that the catalyst was easy to recover by simple filtration from the reaction medium and could be reused without any loss of activity (Table 2, entry 1). We obtained the desired product in 82%, 82%, 80%, 77% yields after 1–4 runs, respectively.

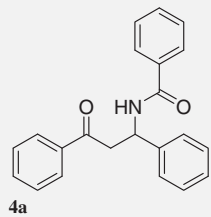
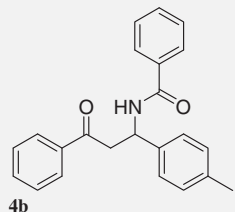
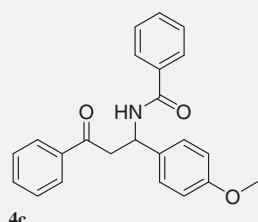
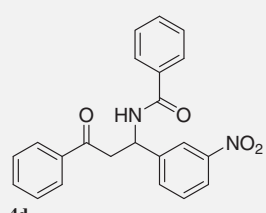
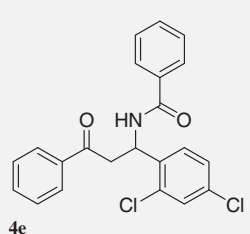
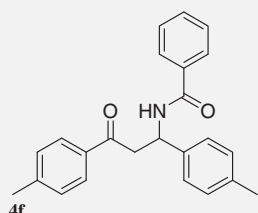
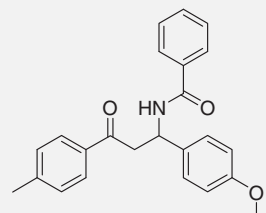
In order to evaluate the generality of the process, several examples illustrate the present method for the synthesis of β-amido ketones **4** was studied (Table 3).²¹

As shown in Table 3, the electronic effect of substituents present on the benzene ring of the aldehyde moiety had a significant effect on the overall yields of the products of β-amido ketones **4**. The substituted aromatic aldehydes, bearing the electro-donating group afforded the corresponding products in good yields. However, under the same reaction conditions, no desired products were obtained when using the aromatic aldehydes carrying strong electron-withdrawing groups as starting materials (Table 3, entries 4, 5 and 17). Furthermore, we also found that the aromatic ketones carrying either the electron-donating or electron-withdrawing substituents could react efficiently giving the products in good yields (Table 3).

Table 2
Optimization of solvents

Entry	Solvent	Temp (°C)	Time (h)	Yield of 4a ^a (%)
1 ^b	EtOH	Reflux	15	82, 82, 80, 77
2	THF	Reflux	24	52
3	Acetonitrile	Reflux	24	28
4	DMF	100	24	22
5	DMSO	100	24	30
6	1,4-Dioxane	100	15	70
7	CCl ₄	Reflux	24	0
8	H ₂ O	100	24	0

^a Isolated yields.^b Catalyst was reused for four times.**Table 3**
Synthesis of β-amido ketones catalyzed by VB₁-Al₂O₃^a

Entry	Product 4	Time (h)	Yield ^b (%)
1		15	82
2		15	84
3		15	83
4		24	0
5		24	0
6		15	82
7		15	81

(continued on next page)

Table 3 (continued)

Entry	Product 4	Time (h)	Yield ^b (%)
8		15	83
9		15	84
10		15	85
11		15	86
12		24	52
13		24	45
14		24	48
15		24	48

Table 3 (continued)

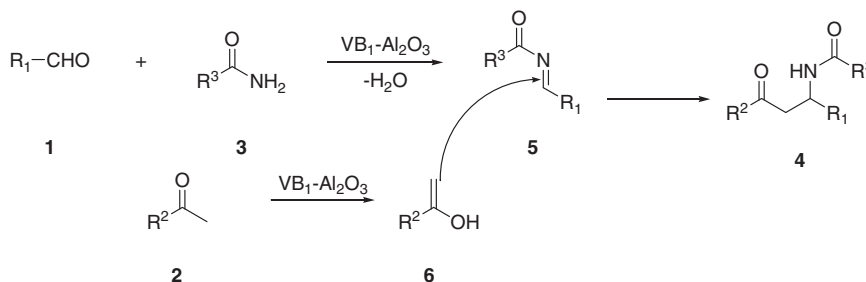
Entry	Product 4	Time (h)	Yield ^b (%)
16		24	52
17		24	0
18		24	0
19		24	0

^a The reaction carried out in EtOH at reflux temperature.^b Isolated yields.

To demonstrate the scope and limitations of the procedure, the condensation of aromatic aldehyde **1**, aromatic ketone **2**, and different amides **3** including aromatic amide, phenylacetamide, acetamide, acrylamide, and *N*-substituted amides, such as *N*-methyl benzamide and caprolactam were carried out in the presence of VB₁-Al₂O₃ in EtOH at reflux temperature for 15–24 h. The results of Table 3 indicated that both aromatic amides (Table 3, entries 1–9) and phenylacetamide (Table 2, entries 10 and 11) worked well, giving high yields of products with little difference. Acetamide and acrylamide afforded relevant lower yields (45–52%). The expected products were obtained in moderate yields under similar conditions. However, the condensation was unsuccessful with *N*-substituted amides. As shown in Table 3 entries 18 and 19, the reaction could not take place when using *N*-substituted amides as the starting materials.

We propose a mechanism of the condensation as shown in Scheme 3. Initially, the condensation between aldehyde **1** and amide **3** gave **5**. Ketone **2** isomerized to **6**, then the Mannich reaction between **5** and **6** furnished the product **4**. We have mentioned previously that the three-component condensation reaction could not proceed smoothly when using the aromatic aldehydes carrying strong electron-withdrawing groups as the starting materials. The probable reason was that it was difficult for these aldehydes to form the intermediate **5**, which meant that the reaction could not proceed smoothly to afford the corresponding products.

In conclusion, we have described a simple and efficient method for one-pot, three-component synthesis of β -amido ketones from aromatic aldehyde, aromatic ketone, and amide in the presence of VB₁-Al₂O₃ as a heterogeneous catalyst. This procedure not only affords the products in good yields but also avoids the problems associated with the catalyst cost, handling safety and pollution. Hence, it is a useful addition to the existing methods.



Scheme 3. Plausible mechanism for the formation of β-amido ketones.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.07.008](https://doi.org/10.1016/j.tetlet.2010.07.008).

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- Preparation of VB₁-Al₂O₃:** The catalyst was prepared by mixing aluminum oxide (9 g, 90 active acidic, 0.063–0.200 mm) with a solution of VB₁ (1 g) in distilled water (15 ml). The suspension was stirred for 1 h at room temperature, followed by removal of water in a rotary evaporator, and the solid powder was dried at 100 °C for 3 h in an oven and then cooled in a desiccator.
- General procedures for the synthesis of β-amido ketones:** A mixture of aldehyde **1** (5 mmol), ketone **2** (5 mmol), amide **3** (5 mmol) and VB₁-Al₂O₃ (0.8 g, 5 mol %) in EtOH (3 mL) was heated to reflux under stirring for 15–24 h. After cooling, EtOAc (30 mL) was added and the catalyst was recovered by simple filtration. The catalyst was rinsed with EtOAc and dried at 100 °C for 3 h, which could be reused without loss of activity. The organic layer was washed with brine, dried over MgSO₄ and concentrated. The crude product residue was purified by chromatography on silica to give pure product **4**.