



## Efficient synthetic method for $\beta$ -enaminones using $\text{SbCl}_3/\text{Al}_2\text{O}_3$ as catalyst under solvent-free conditions

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### ABSTRACT

Antimony trichloride is found to catalyze efficiently the synthesis of  $\beta$ -enaminones on grinding under solvent-free conditions in excellent yields. The use of antimony trichloride on grinding makes this method simple, convenient, eco-friendly and cost-effective.



**Keywords:**  $\text{SbCl}_3/\text{Al}_2\text{O}_3$ ;  $\beta$ -enaminones; solvent-free; grinding.

### INTRODUCTION

Enaminones are known to possess a variety of medicinal properties[1] including anticonvulsant, anti-malarial, anti-inflammatory and cardiovascular properties.[2] The  $\beta$ -enaminones are important precursors for the synthesis of a variety of heterocycles[3] with high pharmaceutical significance. They serve as building blocks for the synthesis of amino esters, amino acids, amino alcohols, peptides and alkaloids.[4] The enamination of 1,3-dicarbonyl compounds to form  $\beta$ -enaminones is an important and widely used transformation in organic chemistry. Several methods are known in the literature for the preparation of  $\beta$ -enaminones. Among them the most commonly used methods involve condensation of 1,3-dicarbonyls with aliphatic and aromatic amines using  $\text{Sc}(\text{OTf})_3$ ,[5]  $\text{Bi}(\text{OTf})_3$ ,[6]  $\text{Au}$ ,[7]  $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ ,[8] silica[9] etc.

Keeping in view the biological importance [1],[2] of  $\beta$ -enaminones, we present here antimony (III) chloride adsorbed on alumina catalyzed mild, efficient and inexpensive procedure for the preparation of  $\beta$ -enaminones from acetylacetone and aromatic amines in solvent-free conditions. A remarkable catalytic effect of antimony (III) chloride was disclosed by Cho's group[10] in hydrophenylation of  $\alpha,\beta$ -unsaturated ketones and aldehydes (Michael-type conjugate addition) with sodium tetraphenylborate in acetic acid.  $\text{SbCl}_3$  has been found to catalyze efficiently the synthesis of 1,2-di-substituted benzimidazoles,[11] benzo[b]-1,4-diazepines,[12] tetra-substituted imidazoles,[13] bis(indolyl)methanes and tris(indolyl)alkanes,[14]  $\alpha$ -aminophosphonates,[15] dihydro pyrimidinones[16] etc.

In continuation of our ongoing efforts into the applications of  $\text{SbCl}_3$  impregnated on inorganic supports as a post transitional Lewis acid in organic synthesis, we wished to employ  $\text{SbCl}_3$  impregnated on  $\text{Al}_2\text{O}_3$ [16] under solvent-free conditions for the synthesis of  $\beta$ -enaminones. The reactions under solvent-free conditions enjoy benefits[17] in terms of easy handling by reducing the pressure development in reaction vessel, simple equipment of operation, less

environmentally hazardous conditions by avoiding use of harmful solvents, time and energy efficiency, low capital outlay for scale up, reduction in the waste produced and by products and formation of cleaner products.

## EXPERIMENTAL SECTION

### General

All experiments were performed in oven dried glass apparatus. Melting points were measured in open capillaries on Perfit melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC using silica gel precoated aluminium sheets. Visualization of spots was effected by exposure to iodine vapours and Dragendroff reagent. Column chromatography was performed on silica gel (60-120 mesh) and compounds were eluted with graded solvent systems of petroleum ether and ethyl acetate. Recrystallization was achieved with ethyl acetate-petroleum ether (60-80) solvent system. IR spectra on KBr were recorded on Perkin-Elmer FTIR spectrophotometer. NMR ( $^1\text{H}$  and  $^{13}\text{C}$  broadband decoupled) and ESIMS spectra were recorded on Bruker Ac-500 (500 & 125 MHz respectively) spectrometer and Micro Mass VG-7070H mass spectrometer respectively. Elemental analysis was performed on Leco CHNS 932 analyzer.  $^1\text{H}$  chemical shifts are reported in parts per million (ppm) from tetra methyl silane (TMS) as internal standard. The abbreviations s, brs, d, dd, t, q, b, m in  $^1\text{H}$  NMR spectra refer to singlet, broad singlet, doublet, double doublet, triplet, quartet, broad and multiplet respectively.

### Preparation of catalyst ( $\text{SbCl}_3 / \text{Al}_2\text{O}_3$ )[16]

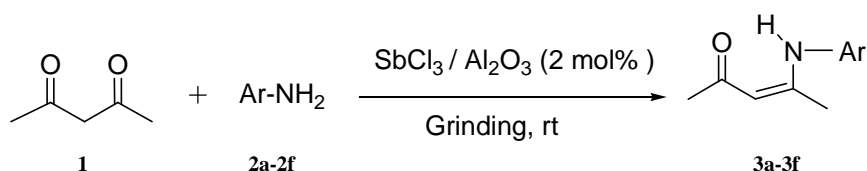
To an antimony (III) chloride (2.28gm, 10 mmol) solution in 100ml of distilled ethanol was added 60 gm of neutral alumina. The mixture was stirred at room temperature for one hour followed by removal of solvent under reduced pressure on rotavapour. The resultant free flowing powder was then activated at  $110^\circ\text{C}$  in an oven for two hours and was used throughout the experimentation.

### General procedure for the synthesis of $\beta$ -enaminones(3a-3f)

A mixture of acetylacetone (5 mmol), aniline **2a-2f** (5.5 mmol) and 2 mol%  $\text{SbCl}_3/\text{Al}_2\text{O}_3$  (0.25 mmol, 0.62g) was grinded using pestle and mortar at room temperature till the completion of reaction (TLC). The reaction mixture was diluted with ethyl acetate (30 ml), washed with water (2 x 10 ml) and brine (1 x 10 ml). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , followed by the removal of ethylacetate under reduced pressure. The residue upon column chromatography gave corresponding  $\beta$ -enaminones **3a-3f** (85-93% yield).

## RESULTS AND DISCUSSION

We herein report an efficient, simple and eco-friendly method for the preparation of  $\beta$ -enaminones by condensation of acetylacetone and aromatic amines in presence of  $\text{SbCl}_3/\text{Al}_2\text{O}_3$  on grinding under solvent-free conditions (Scheme 1).



Scheme 1:  $\text{SbCl}_3/\text{Al}_2\text{O}_3$  catalyzed solvent-free synthesis of  $\beta$ -enaminones on grinding

For optimization of reaction conditions a mixture of acetylacetone (5 mmol, 0.50g), aniline (5.5 mmol, 0.51g) and 5 mol%  $\text{SbCl}_3/\text{Al}_2\text{O}_3$  as catalyst was heated at  $100^\circ\text{C}$  under solvent-free conditions for 2 hours and the yield of the product was 55%. Few other methodologies were also employed like microwave irradiation, stirring, grinding and ultrasonication and the best results were obtained in case of grinding with 82% yield of the product.

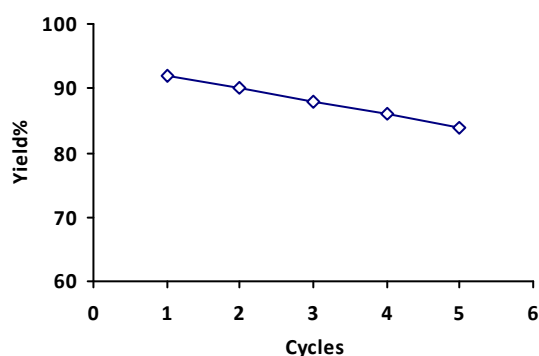
In order to obtain the optimum concentration of catalyst a set of experiments were performed employing different concentrations of  $\text{SbCl}_3/\text{Al}_2\text{O}_3$  for a reaction between 5 mmol acetylacetone and 5.5mmol of aniline and it was observed that 2mol% of catalyst was required to obtain the optimum yield (92%) of the product after one hour of grinding as shown in the Table 1. It has also been observed in one of the experiment devoid of  $\text{SbCl}_3/\text{Al}_2\text{O}_3$ , that the product formation did occur (TLC), but the reaction never went to completion even after 8 hours of grinding.

**Table 1 : Optimization of amount of SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> for synthesis of  $\beta$ -enaminones under solvent-free conditions.<sup>b</sup>**

Entry	Catalyst amount (mol%)	Time(mins) <sup>c</sup>	Yield(%) <sup>d</sup>
1	0	60	20
2	2	60	92
3	5	60	91
4	7	60	90
5	9	60	92

<sup>b</sup> reaction conditions: acetylacetone (5 mmol), aniline (5.5 mmol) and SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub>, grinding, 60 minutes.<sup>c</sup> as revealed by TLC.<sup>d</sup> isolated yield.

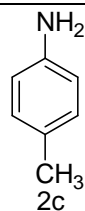
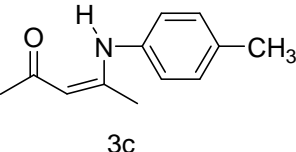
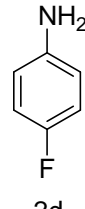
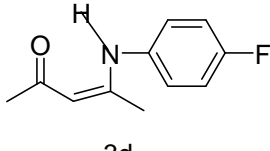
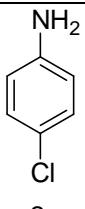
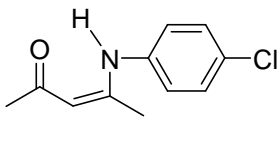
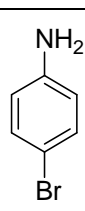
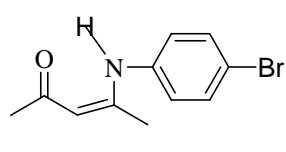
In order to investigate the recyclability, SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> was recovered, activated at 110°C in an oven and reused 5 times, successfully for the reaction of acetylacetone and aniline, no significant decrease in its activity was noticed (Fig.1).

**Fig. 1 Catalyst recyclability**

The condensation of acetylacetone (5 mmol, 0.50g) with aniline, (5.5 mmol, 0.51g) was carried out by grinding using pestle and mortar at room temperature under solvent-free conditions with 2 mol% SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> as catalyst. The product **3a** was characterized by <sup>1</sup>H NMR spectrum [1.99 (s, 3H, -CH<sub>3</sub>), 2.10 (s, 3H, -CH<sub>3</sub>), 5.19 (s, 1H, C=C-H), 7.09-7.31 (m, 5H, Ar-H), 12.49 (br s, 1H, NH)] and supported by IR and Mass data. A characteristic singlet for one alkenic hydrogen at  $\delta$  5.19 arising due to the formation of 4-(phenylamino)-pent-3-en-2-one **3a**. A variety of anilines **2a-2f** were employed with acetylacetone **1** under the same reaction conditions (Scheme 1) and the results are depicted in Table 2.

**Table 2. Substrate scope for the SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> catalyzed preparation of  $\beta$ -enaminones on grinding under solvent-free conditions.<sup>a</sup>**

Entry	Ar-NH <sub>2</sub>	$\beta$ -enaminoketones <sup>b</sup>	Time (min.) <sup>c</sup>	Yield (%) <sup>d</sup>	M.pt(°C)	
					Obs.	Litt. <sup>e</sup>
1			55	92	Oily	Oily[18]
2			53	93	Oily	Oily[18]

Entry	Ar-NH <sub>2</sub>	$\beta$ -enaminoketones <sup>b</sup>	Time (min.) <sup>c</sup>	Yield (%) <sup>d</sup>	M.pt(°C)	
					Obs.	Litt. <sup>e</sup>
3			62	93	66-68	65-67[19]
4			70	86	Oily	Oily[18]
5			68	90	61-62	60-62[18]
6			65	88	59-60	--

<sup>a</sup>reaction conditions: acetylacetone (5 mmol), aniline (5.5 mmol) and SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub>, grinding, 60 minutes.

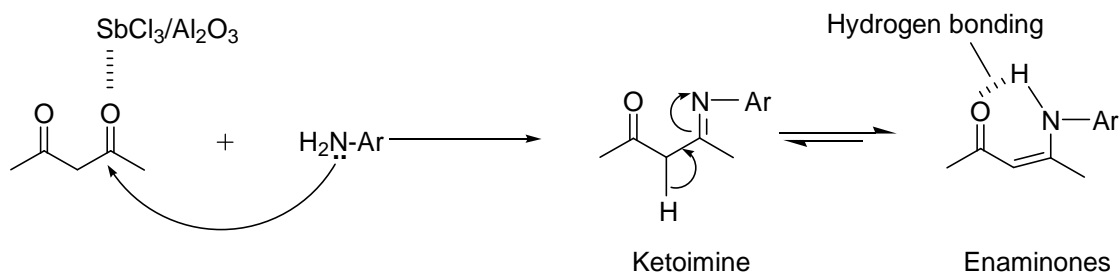
<sup>b</sup>all the products were characterized by their physical and spectral data.

<sup>c</sup>as revealed by TLC

<sup>d</sup>isolated yields.

<sup>e</sup>literature reference of melting point.

To explain the formation of desired product following plausible mechanism is proposed. The formation of  $\beta$ -enaminones simply involves the formation of imine by the condensation of amino group and carbonyl group of different reactants followed by 1,3 H-shift leading to the formation of more stabilized  $\beta$ -enaminones due to intramolecular H-bonding as shown in **Scheme-2**.



**Scheme-2:** Plausible mechanism for the synthesis of  $\beta$ -enaminones

**Spectroscopic data of some  $\beta$ -enaminones (3a-3f)****4-(Phenylamino)-pent-3-en-2-one (3a)**

Viscous oil, Pale yellow, 92% yield, M. pt. Oil [lit.[18] oil].  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) : 1.99 (s, 3H,  $-\text{CH}_3$ ), 2.10 (s, 3H,  $-\text{CH}_3$ ), 5.19 (s, 1H, C=C-H), 7.09-7.31 (m, 5H, Ar-H), 12.49 (br s, 1H, NH).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ): 19.5, 29.0, 126.2, 126.3, 130.7, 133.7, 137.5, 161.1, 196.0. IR KBr;  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 3442, 2997, 1595, 1572, 1509, 1437, 1356, 1281, 1190, 1019, 905, 749, 695. Anal. Calcd for  $\text{C}_{11}\text{H}_{13}\text{NO}$  : C, 75.21; H, 7.65; N, 8.31 Found: C, 75.42; H, 7.42; N, 8.00. ESI-MS:  $m/z$  = 176 (M+H) $^+$ .

**4-(p-Methoxyphenylamino)-pent-3-en-2-one (3b)**

Viscous oil, Pale yellow, 93% yield, M. pt. Oil [lit.[18] oil]  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) : 1.90 (s, 3H,  $-\text{CH}_3$ ), 2.08 (s, 3H,  $-\text{CH}_3$ ), 3.80 (s, 3H,  $-\text{OCH}_3$ ), 5.15 (s, 1H, C=C-H), 6.86 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 7.04 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 12.35 (br s, 1H, NH).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ) : 20.6, 50.1, 55.4, 84.3, 114.2, 126.5, 132.0, 156.5, 161.1, 170.9. IR KBr;  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 3430, 3000, 2829, 1601, 1568, 1355, 1279, 1243, 1194, 1035, 921, 835, 763. Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{NO}_2$  : C, 70.11 ; H , 7.52 ; N , 6.99. Found : C, 70.24 ; H, 7.30 ; N, 6.80. ESI-MS:  $m/z$  = 206 (M+H) $^+$ .

**4-(p-Tolylamino)-pent-3-en-2-one (3c)**

Solid, Pale yellow, M. pt. 66-68 °C (lit.[19] 65-67 °C).  $^1\text{HNMR}$  (500 MHz,  $\text{CDCl}_3$ ) : 1.96 (s, 3H,  $-\text{CH}_3$ ), 2.09 (s, 3H,  $-\text{CH}_3$ ), 2.34 (s, 3H, Ar- $-\text{CH}_3$ ), 5.16 (s, 1H, C=C-H), 6.99 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 7.14 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 12.39 (br s, 1H, NH).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ): 19.9, 29.1, 36.2, 97.8, 120.3, 125.9, 128.4, 151.9, 160.0, 195.5. IR KBr;  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 3424, 3026, 1609, 1565, 1519, 1355, 1282, 1186, 1017, 942, 762. Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{NO}$  : C, 76.01 ; H , 8.11 ; N , 7.59 Found : C, 76.19; H, 7.93 ; N, 7.40. ESI-MS:  $m/z$  = 190 (M+ H) $^+$ .

**4-(p-Fluorophenylamino)-pent-3-en-2-one(3d)**

Viscous oil, Pale yellow, M. pt. Oil [lit.[18] oil],  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) : 1.98 (s, 3H,  $-\text{CH}_3$ ), 2.10 (s, 3H,  $-\text{CH}_3$ ), 5.20 (s, 1H, C=C-H), 7.10 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 7.40 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 12.43 (br s, 1H, NH).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ) : 22.1, 52.6, 87.4, 126.6, 130.1, 138.9, 158.5, 164.3, 173.0. IR KBr;  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 3457, 2995, 1614, 1568, 1504, 1434, 1279, 1189, 1090, 1011, 916, 841, 756. Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{NOF}$  : C, 68.23; H, 6.43 ; N, 7.47. Found : C, 68.39; H, 6.21; N, 7.25. ESI-MS:  $m/z$  = 194 (M+H) $^+$ .

**4-(p-Chlorophenylamino)-pent-3-en-2-one (3e)**

Solid, Pale yellow, M.pt. 61-62 °C (lit.[18] 60-62 °C).  $^1\text{HNMR}$  (500 MHz,  $\text{CDCl}_3$ ) : 1.98 (s, 3H,  $-\text{CH}_3$ ), 2.10 (s, 3H,  $-\text{CH}_3$ ), 5.20 (s, 1H, C=C-H), 7.03 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 7.30 (d,  $J$  = 8.7 Hz, 2H, Ar-H), 12.43 (br s, 1H, NH).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ) : 21.1, 50.6, 86.4, 125.6, 129.1, 137.9, 158.5, 162.3, 171.0. IR KBr;  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 3456, 2994, 1613, 1567, 1503, 1434, 1278, 1189, 1090, 1011, 915, 840, 755. Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{NOCl}$  : C, 62.75; H, 5.92 ; N, 6.91. Found : C, 63.00; H, 5.73; N, 6.68. ESI-MS:  $m/z$  = 212(M+2), 210 (M+H) $^+$ .

**4-(p-bromophenylamino)-pent-3-en-2-one (3f)**

Solid, Pale yellow. M. pt. 59-60 °C,  $^1\text{HNMR}$  (500 MHz,  $\text{CDCl}_3$ ) : 1.96 (s, 3H,  $-\text{CH}_3$ ), 2.09 (s, 3H,  $-\text{CH}_3$ ), 5.18 (s, 1H, C=C-H), 7.01 (d,  $J$  = 8.3 Hz, 2H, Ar-H), 7.29 (d,  $J$  = 8.3 Hz, 2H, Ar-H), 12.42 (br s, 1H, NH).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ) : 21.0, 50.4, 86.3, 125.3, 129.0, 137.6, 158.2, 162.1, 170.0. IR(KBr) $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 3457, 2997, 1617, 1569, 1506, 1437, 1280, 1191, 1093, 1014, 918, 843, 756. Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{NOBr}$  : C, 51.99; H, 4.76 ; N, 5.51. Found : C, 50.73; H, 4.19; N, 4.95. ESI-MS:  $m/z$  = 256(M+2), 254 (M+H) $^+$ .

**CONCLUSION**

In summary we developed an efficient and solvent free synthesis of  $\beta$ -enaminones catalysed by  $\text{SbCl}_3/\text{Al}_2\text{O}_3$ .

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