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SOLVENT-FREE SYNTHESIS OF β-ENAMINOESTERS USING ANTIMONY(III) CHLORIDE ON ALUMINA ($SBCL_3/AL_2O_3$) AS LEWIS ACID CATALYST

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Abstract

The efficient catalytic synthesis of β-enaminoesters can be accomplished through the use of antimony trichloride. This reaction can occur *via* grinding, without the need for a solvent, and results in high yields of the product that is needed. The application of antimony trichloride in the grinding process renders this technique straightforward, convenient, environmentally sustainable, and economically advantageous.

Keywords: Aniline; catalyst recyclability; grinding; Lewis acid; methyl acetoacetate.

Introduction

Enaminoesters have been documented for possessing a range of therapeutic qualities, such as anticonvulsant, anti-malarial, anti-inflammatory, and cardiovascular effects [1,2]. The β-enaminoesters possess significant significance as precursors in the synthesis of several heterocycles [3] that exhibit significant therapeutic relevance. These compounds contribute as key components for the production of amino esters, amino acids, amino alcohols, peptides, and alkaloids [4]. The transformation of 1,3-dicarbonyl compounds into β-enaminoesters through enamination is a fundamental and extensively employed process within the field of organic chemistry. A variety of techniques have been documented in research literature for the synthesis of β-enaminoesters. Among the several methods available, the most often employed techniques entail the condensation of 1,3-dicarbonyls with aliphatic and aromatic amines with catalysts such as $Sc(OTf)_3$,[5] $Bi(OTf)_3$ [6], Au [7], $Zn(OAc)_2.2H_2O$ [8], and silica [9].

Enaminoesters have drawn considerable attention in the field of organic synthesis, particularly in the production of various N-heterocycles such as alkaloids. This interest emerges from their inherent polyfunctionality, since they possess a nitrogen atom, a double bond, and an ester moiety concurrently. This peculiar combination offers the opportunity for side chain elongation or ring closure, thus allowing the synthesis of complex molecular structures. The β-enaminoester functional group is extremely beneficial in the synthesis of nitrogen-containing fused bicyclic compounds, such as indolizidine or pyrrolizidine alkaloids. A significant number of these compounds exhibit chirality at the α- and β-position relative to the nitrogen atom. *N*-heterocycles can be synthesized *via* the cyclization of enaminoesters derived from a chemical reaction between 1,3-dicarbonyl compounds and amines.

In consideration of the vital biological significance [10,11] of β-enaminoesters, we hereby present a method employing antimony (III) chloride adsorbed on alumina as a catalyst for the mild, efficient, and economical synthesis of β-enaminoesters. This procedure incorporates the condensation of methyl acetoacetate and aromatic amines under solvent-free conditions. The catalytic effect of antimony (III) chloride in the hydrophenylation of α,β-unsaturated ketones and aldehydes (namely, Michae-type conjugate addition) with sodium tetraphenylborate in acetic acid was reported by Cho's research group [12]. $SbCl_3$ has been reported to have high catalytic efficiency in the synthesis of many compounds, including 1,2-di-substituted benzimidazoles,[13] benzo[b]-1,4-diazepines,[14] tetra-substituted imidazoles [15], bis(indolyl)methanes and tris(indolyl)alkanes [16], α-aminophosphonates [17] and dihydro pyrimidinones [18].

As part of our ongoing research on the utilization of $SbCl_3$ impregnated on inorganic substrates as a post-transitional Lewis acid in organic synthesis, we aimed to utilize $SbCl_3$ impregnated on Al_2O_3 [18] under solvent-free conditions for the synthesis of β-enaminoesters. The application of solvent-free conditions in reactions offers several advantages [19]. These include ease of handling owing to reduced pressure development in the reaction vessel, simplified operation equipment, environmentally conscious conditions by eliminating the use of harmful solvents, improved time and energy efficiency, lower the expenditure for scaling up, declined waste production and byproduct formation, and the generation of cleaner products.

EXPERIMENTAL SECTION

General

The experiments were carried out using oven dried glass apparatus. The melting points have been determined using the Perfit melting point apparatus, with observations taken via open capillaries. The advancement of the reaction was observed through the application of thin-layer chromatography (TLC) using

silica gel precoated aluminum sheets. The visualization of spots was affected by the exposure to iodine vapours and the Draggendroff reagent. The experiment involved the utilization of column chromatography using silica gel (60-120 mesh) as the stationary phase. The substances were separated by eluting them with solvent systems consisting of petroleum ether and ethyl acetate in a graduated manner. The process of recrystallization was successfully conducted using a solvent solution consisting of ethyl acetate and petroleum ether (60-80). In this study, infrared spectra were obtained using potassium bromide (KBr) as the sample matrix. The data acquisition was performed using a Perkin-Elmer Fourier transform infrared (FT IR) spectrophotometer. Nuclear Magnetic Resonance (NMR) spectra, specifically ^{1}H and ^{13}C broadband decoupled, were acquired using a Brucker Ac-500 spectrometer operating at 500 MHz and 125 MHz, respectively. Additionally, Electrospray Ionization Mass Spectrometry (ESIMS) spectra were obtained using a Micro Mass VG-7070H mass spectrometer. The Leco CHNS 932 analyser was utilized to do elemental analysis. Chemical shifts of 1H nuclei are often expressed in parts per million (ppm) relative to tetramethylsilane (TMS), which serves as the internal reference. The acronyms "s," "brs," "d," "dd," "t," "q," "b," and "m" in ^{1}H NMR spectra correspond to the following spectral characteristics: singlet, broad singlet, doublet, double doublet, triplet, quartet, broad, and multiplet, respectively.

Preparation of catalyst ($SbCl_3$ / Al_2O_3)[18]

A solution containing 2.28 grams (10 millimoles) of antimony (III) chloride was prepared in 100 milliliters of distilled ethanol. Subsequently, 60 grams of neutral alumina were added to the solution. The mixture was stirred regularly at ambient temperature for a duration of one hour, after which the solvent was eliminated through the application of reduced pressure using a rotary evaporator. The resulting powder, which exhibited a free-flowing characteristic, was afterwards subjected to activation at a temperature of 110 °C within an oven for a duration of two hours. This activated powder was utilized throughout the course of the experimentation.

General procedure for the synthesis of β-Enaminoesters (3a-3e)

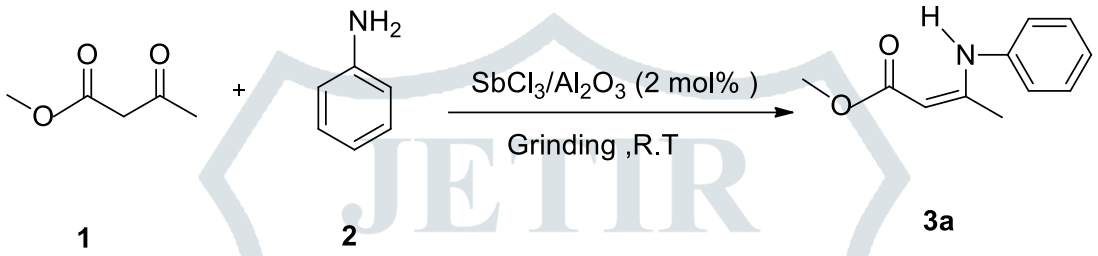
A mixture of methyl acetoacetate (5 mmol), aniline (5.5 mmol) and 2 mol % $SbCl_3/Al_2O_3$ (0.25 mmol, 0.62g) was grinded using pestle and mortar at room temperature till the completion of reaction (TLC). The reaction mixture was diluted with ethyl acetate (30 ml), washed with water (2 x 10 ml) and brine (1 x 10 ml). The organic layer was dried over anhydrous Na_2SO_4, followed by the removal of ethylacetate under reduced pressure. The residue upon column chromatography gave corresponding β-enaminoesters (**3a-3e**) (85-93% yield).

For optimization of reaction conditions, a mixture of methyl acetoacetate (5 mmol, 0.50g), aniline (5.5 mmol, 0.51g) and 5 mol% $SbCl_3/Al_2O_3$ as catalyst was heated at 100 °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.

Results and discussions

In this study, we present a highly effective, straightforward, and environmentally sustainable approach for synthesizing β-enaminoesters. This process involves the condensation of methyl acetoacetate and aromatic amines in the presence of $SbCl_3/Al_2O_3$ catalyst, utilizing a solvent-free conditions. The condensation of methyl acetoacetate, **1** (5 mmol, 0.58g) with aniline, **2** (5.5mmol, 0.51g) was carried out by grinding using pestle and mortar at room temperature under solvent free conditions with 2 mol% $SbCl_3/Al_2O_3$ as catalyst **(Scheme 1).**



Scheme 1 Synthesis of β-enaminoester via the condensation of methyl acetoacetate and aniline.

In order to obtain the optimum concentration of catalyst a set of experiments were performed employing different concentrations of $SbCl_3/Al_2O_3$ for a reaction between 5 mmol acetylacetone and 5.5 mmol of aniline and it was observed that 2 mol % 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 $SbCl_3/Al_2O_3$, 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 $SbCl_3/Al_2O_3$ for synthesis of β-enaminones under solvent-free conditions.[b]

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

[b] reaction conditions: acetylacetone (5 mmol), aniline (5.5 mmol) and $SbCl_3/Al_2O_3$, grinding, 60 minutes.
[c] as revealed by TLC.
[d] isolated yield.

In order to investigate the recyclability, $SbCl_3/Al_2O_3$ 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**).

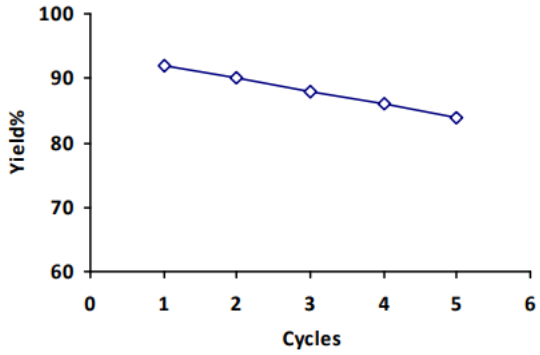
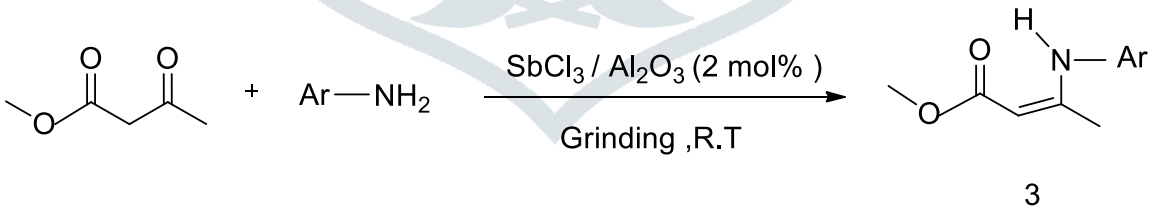


Fig. 1. Catalyst recyclability

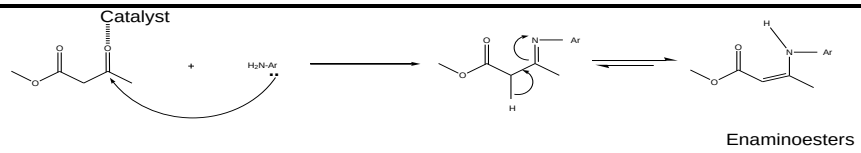
After one hour, the formation of product was noticed on TLC (Eluent, ethyl acetate: petroleum ether = 1:4) with Rf-value 0.8. After the completion of reaction, the product was isolated and purified by column chromatography in 88% yield. The structure of product was established by spectral means such as ^{1}H NMR, ^{13}C NMR, IR and MS. Its ^{1}H NMR showed a characteristic singlet for one alkenic hydrogen at δ 4.7 arising due to the formation of methyl-3-(phenylamino)-but-2-enoate, **3a**. The presence of singlet at δ 1.99 and another singlet at δ 3.68 correspond to methyl and methoxy protons respectively. Moreover, a multiplet at δ 7.07-7.30 corresponded to five protons of phenyl ring. The IR-spectrum showed diagnostic bands at 3247 cm^{-1} (υ N-H) and 1651cm^{-1} (υ C=O). These features coupled with mass spectrum unambiguously established the identity of product as methyl-3-(phenylamino)-but-2-enoate, **3a**.

A variety of anilines were employed under the same reaction conditions (**Scheme 2)** and the results are depicted in **Table 2.**



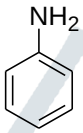
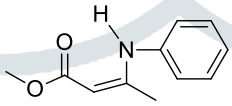
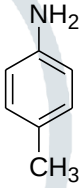
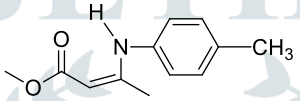
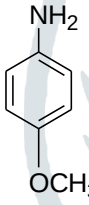
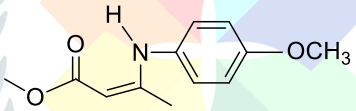
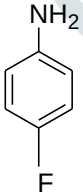
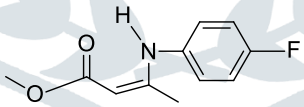
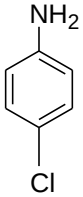
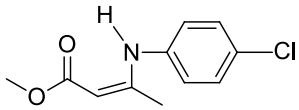
Scheme 2 General synthesis of β-enaminoester *via* the condensation of methyl acetoacetate and aromatic amines.

In order to elucidate the steps through which the desired product is formed, a plausible mechanism is proposed. The synthesis of β-enaminoesters involves the condensation of an amino group and a carbonyl group from different reactants, resulting in the formation of an imine. Subsequently, a 1,3 H-shift occurs, leading to the formation of β-enaminoesters with enhanced stability due to intramolecular hydrogen bonding, as seen in **Scheme 3**.



Scheme 3 Mechanism of synthesis of β-enaminoester.

Table 2 (Synthesis of β-enaminoesters)

Entry	Ar-NH_2	β-enaminoesters 3	Time (min.)	Yield(%)
1.		 **3a**	80	88
2.		 **3b**	76	89
3.		 **3c**	70	90
4.		 **3d**	90	88
5.		 **3e**	86	87

All the synthesized compounds (**3a-e**) were characterised using different physical and spectroscopic techniques including physical state colour and melting point and, FT IR, ^{1}H NMR, ^{13}C NMR and ESI MS spectroscopy, respectively.

1. Methyl-3-(phenylamino)-but-2-enoate (3a)

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.01; H, 6.99; N, 7.53; **Found:** C, 69.10; H, 6.80; N,7.33.

Physical state: Viscous oil; **Colour:** Pale yellow; **Melting point :** Oil [lit[66] oil]; **IR(KBr)υ_{max} /cm^{-1}:** 3247, 2992, 1651, 1589, 1483, 1435, 1356, 1260, 1162, 1055, 786; **^{1}H NMR (500 MHz, $CDCl_3$) :** 1.99 (s, 3H, -CH_3), 3.68 (s, 3H, -OCH_3), 4.7 (s, 1H, C=C-H), 7.07-7.30 (m, 5H, Ar-H), 10.36 (br s, 1H, NH); **^{13}C NMR ($CDCl_3$, 125 MHz):** 20.2, 50.2, 85.6, 124.4, 125.0, 129.0, 139.3, 159.0, 170.0.; **ESI-MS : m/z** = 192 $(M+H)^+$.

2. Methyl 3-(*p*-tolylamino)-but-2-enoate (3b)

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.02; H, 7.65; N, 7.05; **Found:** C, 70.22; H, 7.37; N,6.82;

Physical state: Viscous oil; **Colour:** Pale yellow; **Melting point :** Oil [lit[66] oil]; **IR(KBr)υ_{max} /cm^{-1}:** 3263, 2949, 1651, 1598, 1489, 1384, 1360, 1275, 1187, 1162, 1058, 913, 787; **^{1}H NMR (500 MHz, $CDCl_3$) :**1.95 (s, 3H, -CH_3), 2.33 (s, 3H, Ar-CH_3), 3.68 (s, 3H, -OCH_3), 4.66 (s, 1H, C=C-H), 6.97 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.12 (d, *J* = 8.1 Hz, 2H, Ar-H), 10.25 (br s, 1H, NH); **^{13}C NMR ($CDCl_3$, 125 MHz) :** 20.1, 20.8, 50.1, 85.0, 124.7, 129.6, 130.8, 136.6, 159.4, 170.7; **ESI-MS: *m*/*z*** = 228 $(M+Na)^+$.

3. Methyl 3-(*p*-methoxyphenylamino)-but-2-enoate (3c)

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 64.92; H, 7.18; N, 6.54; **Found:** C, 65.16; H, 6.97; N,6.33;

Physical state: Viscous oil; **Colour:** Pale yellow; **Melting point :** Oil [lit[66] oil]; **IR(KBr)υ_{max} /cm^{-1}:** 3270, 2943, 2844, 1701, 1597, 1515, 1486, 1435, 1243, 1162, 1029, 1008, 785; **^{1}H NMR (500 MHz, $CDCl_3$):** 1.91 (s, 3H, -CH_3), 3.67 (s, 3H, -OCH_3), 4.65 (s, 1H, C=C-H), 6.86 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.02 (d, *J* = 8.7 Hz, 2H, Ar-H), 10.12 (br s, 1H, NH); **^{13}C NMR ($CDCl_3$, 125 MHz):** 20.0, 50.1, 55.4, 84.3, 114.2, 128.8, 132.0, 157.5, 160.1, 170.7; **ESI-MS: *m*/*z*** = 244 $(M+ Na)^+$.

4. Methyl 3-(*p*-fluorophenylamino)-but-2-enoate (3d)

Anal. Calcd for $C_{11}H_{12}NO_2F$: C, 62.91 ; H, 5.93; N, 6.97; **Found**: C, 63.15 ; H, 5.70; N,6.70; **Physical state:** Viscous oil; **Colour:** Pale yellow; **Melting point :** Oil [lit[66] oil]; **IR(KBr)υ_{max} /cm^{-1}:** 3272, 2948, 1654, 1593, 1487, 1353, 1271, 1165, 1060, 940, 787, 700; **^{1}H NMR (500 MHz, $CDCl_3$) :** 1.91 (s, 3H, -CH_3), 3.70 (s, 3H, -OCH_3), 4.68 (s, 1H, C=C-H), 7.07 (d, *J* = 8.5 Hz 2H, Ar-H), 7.30 (d, *J* = 8.5 Hz 2H, Ar-H), 10.24 (br s, NH); **^{13}C NMR (125MHz, $CDCl_3$):** 20.0,58.7,85.8, 115.3, 135.2, 159.0, 160.2, 170.4; **ESI-MS: *m*/*z*** = 210 $(M+H)^+$.

5. Methyl 3-(p-chlorophenylamino)-but-2-enoate (3e)

Anal. Calcd. for C11H12NO2Cl: C, 58.25; H, 5.60; N, 6.52; **Found:** C, 58.54; H, 5.36; N,6.21;

Physical state: Solid; **Colour:** Pale yellow; **Melting point:** 60-61 ºC (lit. 59-600C); **IR(KBr)υmax /cm^{-1}:** 3273, 2949, 1653, 1592, 1487, 1352, 1270, 1166, 1059, 941, 787, 702;

^{1}H NMR (500 MHz, $CDCl_3$) : 1.98 (s, 3H, -CH3), 3.68 (s, 3H, -OCH3), 4.72 (s, 1H, C=C-H), 7.01 (d, J = 8.4 Hz, 2H, Ar-H), 7.28 (d, J = 8.4 Hz, 2H, Ar-H), 10.33 (br s, 1H, NH); **^{13}C NMR (125 MHz, $CDCl_3$):** 20.1, 50.3, 86.4, 125.5, 129.1, 137.9, 158.5, 162.3, 170.6; **ESI-MS:** m/z = 228(M+2), 226 $(M+H)^+$ [in the ratio of 1:3].

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