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**Research Article**

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# A facile synthesis of (±)-Baclofean *via* $Fe(acac)_3$ catalyzed Michael addition and Pinner reaction

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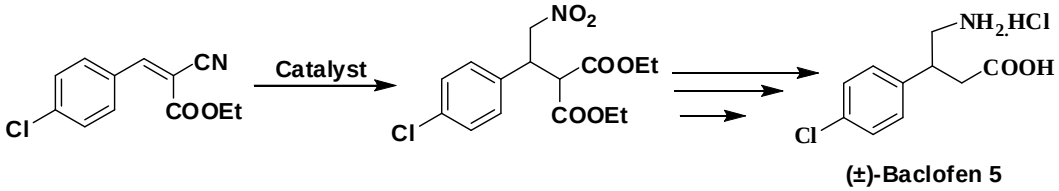
**ABSTRACT**

*An effective and convenient procedure for the Michael addition using Fe $(acac)_3$ (1 mol %) as an effective catalyst, catalyses the Michael addition reaction of nitro methane to α-cyano cinnamate ester followed by Pinner reaction to produce corresponding diethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate with good yields under mild condition with high yield. Accordingly, we applied this synthetic strategy for synthesis of* ***(±)****-Baclofean.*




**(±)-Baclofen 5**

*Michael addition of nitromethane to an α-cyano cinnamate ester is a key step for the synthesis of (±)-baclofen.*

**Keywords:** Michael addition; $Fe(acac)_3$, Nitro methane; α-Cyano cinnamic ester, Amino acids.

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## INTRODUCTION

The transition metal(TM) catalysis plays an important role in modern organic chemistry [1]. The most of the reaction catalyzed by Lewis acid are stoichiometric therefore, recently have great attention towards the transition metal catalyzed reaction in synthetic chemistry due to their numerous advantages low cost, nontoxic or interesting catalytic activity, reaction proceed cleanly with high efficiency and easy to handle, at ambient reaction condition without formation of salt. Although precious metal catalysts have their own impact on the field, alternatively non-precious metals like Cu, Co, Ce, Ni and Fe are emerging as important catalysts. To access C-C bonds, novel transition metal complexes or salts have previously been used as catalysts. Iron is well known as one of the most abundant and cheapest metal. However, the use of Iron salt as important Lewis acid in organic transformation such as the homo coupling [2], Grignard reaction [3], alkylation [4], alkenylation of organo manganese [5], aryl coupling reaction [6], N-Arylatation [7], C-N bond cleavage [8] and Michael addition [9] *etc*.

Michael addition reaction is one of the most useful methods for the formation of C-C bonds. Many asymmetric variants exist for the Michael addition to nitroalkenes has been developed as a powerful tool in organic synthesis [9], because Michael adducts of nitroalkanes are versatile building blocks in agricultural and pharmaceutical industry. In particular, α,β-unsaturated ketone and ester are versatile acceptors for the synthesis of γ-amino acids, amino

carbonyls and amino alcohol. Although, there have been many reports of enantioselective Michael additions using chiral catalysts, including metal-based catalysts, multimetallic catalysts as well as organic catalysts and optically active thiourea as efficient catalysts.

Traditionally, esterifications of nitriles and ester have considerable attention due to their biological activity and their presence in a variety of significant natural products. Consequently, a number of synthetic strategies have been reported for the esterification of nitriles [10], there are a continuous demand, novel and selective catalyst for the transformation of nitrile to ester. One-pot esterification of nitriles with alcohols may provide an attractive alternative method for ester formation. Moreover, in the modern organic synthesis, the transformation of nitriles into esters is potentially useful [11]. Murahashi et al. first reported an efficient Ru complex catalyst for direct esterification of nitriles under neutral conditions [12].

In mammalians [13], γ-Amino butyric acid (GABA) plays an important role as an inhibitory neurotransmitter in the central nervous system (CNS) and the deficiency of GABA is associated with diseases that exhibit neuromuscular dysfunctions such as epilepsy, Huntington's and Parkinson's diseases *etc*. Baclofen is a lipophilic analogue of GABA, and widely used as antispastic agent. Although baclofen is commercialized in its racemic form, it has been reported that its biological activity resides exclusively in the (*R*)-enantiomer. We next applied enantioselective Michael reaction for the synthesis of (*R*)-(-)-Baclofen. The γ-butyrolactam (pyrrolidin-2-one or γ-lactam) skeleton exists throughout nature and is present in many bioactive natural products. It also serves as a key intermediate in the synthesis of biologically and pharmaceutically useful molecules such as (*R*)-baclofen and (*R*)-rolipram [14].

However, we are first time demonstrating that the use of $Fe(acac)_3$ catalyst for Michael addition reaction followed by Pinner reaction [15] of nitromethane on α-Cyano cinnamic ester. We first intended to Michael addition reaction of Nitromethane to an α,β-unsaturated Cinnamate ester with a more favorable substitute as a test reaction for optimization. We used the $Fe(acac)_3$ catalyst for Michael addition reaction of nitro methane on α-cyano Cinnamate ester component in ethanol as solvent (**Scheme 1**).

## EXPERIMENTAL SECTION

All reactions were carried out in dry solvents, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Kieselgel 60 $F_{254}$, Merck). Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in 2, 4-dinitrophenylhydrazine/ anisaldehyde and charring on hot plate. All products were characterized by $^1$H NMR and $^{13}$C NMR, IR, Mass and Elemental analysis. $^1$H NMR and $^{13}$C NMR were recorded on Varian Mercury 300 MHz spectrometer. Chemical shifts are expressed in ppm values and $^1$H NMR spectra are referenced to 0.00 ppm for $Me_4Si$ (TMS) and $^{13}$C NMR spectra are referenced to 77.00 ppm for $CDCl_3$. Peak multiplicities are designated by the following abbreviations: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant in Hz. IR spectra were obtained on a Shimadzu FTIR-8400 with samples loaded as thin films on KBr plate, neat or with $CH_2Cl_2$ as indicated. Mass spectra were recorded at an ionization potential of 70 eV; Elemental analyses were recorded on Flash E. A. 1112 Thermo instrument. Melting points recorded are uncorrected. Column chromatography on silica gel (300-400 mesh) was performed with reagent grade ethyl acetate and hexane as an eluent.

Typical experimental procedure: A mixture of α-Cyano cinnamic ester (193 mg, 0.82 mmol), $Fe(acac)_3$ (1 mol %) in EtOH (2 mL) were stirred at room temperature. Nitro methane (4.00 mmol) was added and reaction mixture was further reflux and stirred for 6.0h. After completion of reaction remove the volatile impurities under reduced pressure gave a crystalline crude product and diluted with water. The reaction mixture was extracted with EtOAc (2 X 20mL) and organic layer was washed with brine and dried with $Na_2SO_4$. Evaporation of solvent furnished the crude product that was purified by column chromatography over silica gel using EtOAc in petroleum ether to give pure product. Known compounds and were identified by spectroscopic data (IR, $^1$H, $^{13}$C NMR, GCMS) and are in good agreement with those of the reported. The spectroscopic and analytical data of new products whose spectroscopic data are not readily available are provided here in order of their below.

**diethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate(3b)**

Yield 89%. Colorlesss solid m.p. 56-58 °C IR (KBr) 3057, 2985, 1737, 1558, 1397, 1265, 1170, 1024,740. $cm^{-1}$ $^1$H-NMR (300 MHz, $CDCl_3$) δ. 7.30 (d, 2H, *J* = 8.2 Hz), 7.19 (d, 2H, *J* = 8.2 Hz), 4.84 (dd, 1H, *J* = 4.9, 13.2 Hz), 4.75(dd, 1H, *J* = 9.6, 12.9 Hz ) 4.18-4.10 (m, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 3.77 (d, 1H, *J* = 9.6 Hz ), 1.25 (t, 3H, *J* =

7.15 Hz), 1.06 (t, 3H, *J* = 7.15 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.81, 166.21, 134.36, 133.77, 129.07, 128.66, 61.84, 61.58, 54.24, 41.89, 1349, 13.30 MS (m/z ) 366.16 ($M^+$ +Na).

**4-(4-chlorophenyl) pyrrolidin-2-one(4)**

Yield 70%. Colorlesss solid m.p.188-189°C; IR (KBr) 3433, 3230, 3017, 2360, 1715, 1685, 1493. $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) δ. 7.33 (d, 2H, *J* = 8.8 ), 7.19 (d, 2H, *J* = 8.8 ), 3.80 (apt, t, 1H, *J* = 8.8 Hz), 3.74-3.63 (m, 1H) , 3.37-3.42 (dd, 1H, *J* = 7.1, 8.8 Hz) 2.81-2.72 (dd, 1H, *J* = 8.8, 17.0 Hz), 2.52-2.71 (dd, 1H, *J* = 8.2, 17.0 Hz). ppm $^{13}$C NMR (75 MHz, $CDCl_3$) δ 175.46, 138.28, 136.95, 133.32, 129.32, 128.25, 127.81, 43.75, 39.91, 38.18.

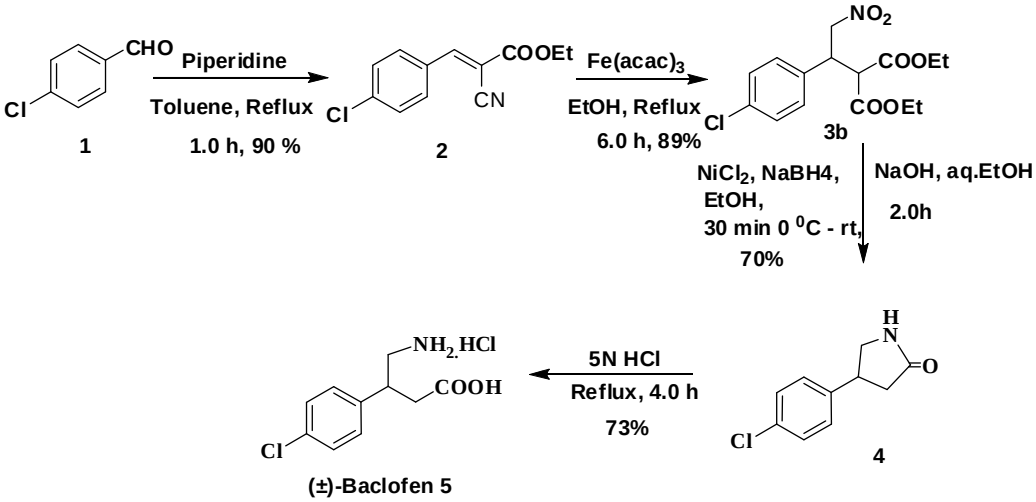
**4-amino-3-(4-chlorophenyl)butanoic acid hydrochloride(5)**

Yield 73%. Colorlesss solid m.p. 109-111 °C; $^{1H}$-NMR (300 MHz, $D_2O$) δ. 7.33 (d, 2H, *J* = 8.8 ), 7.19 (d, 2H, *J* = 8.8 ), 3.80 (apt, t, 1H, *J* = 8.8 Hz), 3.74-3.63 (m, 1H), 3.37-3.42 (dd, 1H, *J*= 7.1, 8.8 Hz) 2.81-2.72 (dd, 1H, *J* = 8.8, 17.0 Hz), 2.52-2.71 (dd, 1H, *J* = 8.2, 17.0 Hz). ppm $^{13}$NMR (75 MHz, $D_2O$) δ 178.50, 140.61, 132.87, 128.97, 128.06, 49.49, 39.65, 37.85.

## RESULTS AND DISCUSSION

As part of our ongoing research program herein, we wish to report on a new catalyst for Michael addition. However, we are first time demonstrating that the use of $Fe(acac)_3$ as a catalyst for Michael addition of nitromethane on α-Cyano cinnamic ester **2** furnished the **3b** with good yield at ambient reaction condition in 1.0h **(Scheme 1).** ). This reaction mixture contains 3a as the respective ester and **3b** is simply detected by thin-layer chromatography (TLC). Furthermore, increase the course of reaction time 3b as a sole product; this is a key intermediate for synthesis (±)-Baclofen.

The present catalytic strategy for the synthesis of (±)-Baclofen is as outlined in the (**Scheme 1).** Accordingly, started from Knoevenagel condensation [16] 4-chlorobenzyladehyde with ethyl cyanoacetate to get α-Cyano cinnamic ester. Reaction of 5 equiv of nitromethane with α-Cyano cinnamic ester in presence of the catalytic quantity 1 mol% of $Fe(acac)_3$ in ethanol with stirring for 6.0h produced the crystalline Michael adduct is diethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate(**3b**) with 89% yield. The reduction of **3b** containing nitro group can be reduced with sodium borohydride, in presence of nickel chloride in EtOH 0ºC to 25 °C 1.0h. It resulted in the formation of intermediate amine which subsequently cyclise to generate pyrrolidine moiety and followed, by hydrolysis ester group with aq.NaOH, finally pyrrolidine moiety hydrolyzed with 5N HCl affording pure (±) Baclofen **5** its hydrochloric Salt. (±) Baclofen act as a neurotransmitter inhibitor drug molecule**.** Using this synthetic strategy, (±) Baclofen was obtained in four steps with an overall yield 40.93%.




**Scheme: 1**

## CONCLUSION

In summary, we have developed an environmentally friendly Michael addition of nitro methane on α-Cyano cinnamic ester in the presence of transition metal catalyst at ambient reaction condition without formation of salt. The method have been applied successfully for synthesis of (±)-baclofen *via* novel Pinner reaction. (±) Baclofen was obtained in four steps with an overall yield 40.93%. An advantage of this synthetic strategy includes simple catalyst, mild reaction, shorter reaction times and easy work-up procedure.

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