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Der Chemica Sinica, 2012, 3(1):231-235

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

# 3-Nitrophenylboronic acid-catalyzed synthesis of β-enaminones under solvent-free conditions

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**ABSTRACT**

*An efficient synthesis of β-enaminones from amines with β-keto esters in good yield using 3-nitrophenylboronic acid as mild and environmentally benign catalyst under solvent-free conditions at ambient temperature is described.*

**Keywords:** Amines, β-keto esters, β-enaminones, 3-nitrophenylboronic acid, solvent-free conditions.

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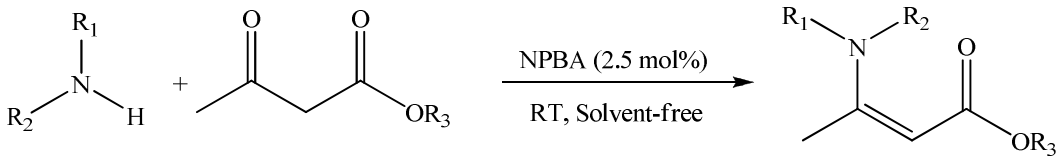
## INTRODUCTION

β-Enaminones are an important class of compounds used for selective alkylation and acylation of carbonyl compounds and are valuable intermediates for the synthesis of biologically active natural products [1]. Also these compounds are useful precursors for the synthesis of variety of heterocyclic compounds [2], which have been used in pharmaceuticals [3] and are building blocks for the synthesis of amino acids [4], peptides [5] or alkaloids [6]. In addition, chiral enaminones obtained from optically active compounds are useful ligand for diastereoselective synthesis [7].

β-Enaminones compounds can be obtained *via* amide enolates to nitriles [8], tosyl imines [9], addition of enamines to activated carboxylic acid derivatives [10] and also synthesized by direct condensation of β-keto esters with amines [11]. The synthesis of β-enaminoester using phosphonium ionic liquids as catalyst from ethyl acetoacetate and ammonium acetate in acetonitrile is reported [12].

Organo-boron compounds are recently attracted much more attention in synthetic organic chemistry and has been successfully used as a catalyst in organic transformation as effective Lewis acid for several synthetic process such as amidation of carboxylic acids, Diels-Alder cyclo-additions [13] and enantioselective allylation reaction [14], synthesis of 3,4-dihydropyrimidinones [15] and synthesis of 1,4-dihydropyridines [16].




**1** **2** **3**

**Scheme 1.** Synthesis of β-enaminones catalysed by 3-nitro phenylboronic acid (NPBA) under solvent-free conditions.

As part of our continuing research on 3-nitrophenylboronic acid [16-17] to describe a mild and efficient method for the synthesis of β-enaminone derivatives using 3-nitrophenylboronic acid as a novel Lewis acid catalyst. This method is not only provides an excellent complement to synthesize β-enaminones but also avoids the use of

hazardous acids or bases and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive solvents, reagents and catalyst under mild conditions and experimental operational ease which enhances the isolated yield to level of 83-95%.

## MATERIALS AND METHODS

### Experimental

All chemicals were purchased from Sigma-Aldrich chemical companies. The progress of the reactions was followed by TLC using silica gel Merck 60 $F_{254}$ plates. Melting points were recorded on open capillaries and are uncorrected. IR spectra were recorded on Varian FTIR spectrophotometer using KBr discs. $^1$H NMR spectra were recorded on a Varian 300 MHz spectrometer using $CDCl_3$ as solvent.

***General procedure:***

A mixture of amine **1** (1 mmol), β-keto ester **2** (1 mmol) and 3-nitro-phenylboronic acid (2.5 mol %) was stirred at room temperature for 2 h. After completion of the reaction (TLC), the reaction mixture was quenched with water 20 ml and extracted with dichloromethane (3x10 mL). The organic layer was washed successively with saturated sodium bicarbonate, brine and finally with water, dried over anhydrous $Na_2SO_4$ and concentrated. The crude product residue was purified by filtration on short silica gel column pretreated with triethyl amine to give pure product **3**.

### Spectral Data

**4-Phenylamino-pent-3-en-2-one (3a):** (white solid); MP 51 ◦C; IR (cm$^{-1}$) 3452, 3040, 3029, 1631, 1580, 1515, 1289, 1194, 1035, 937, 766, 710; $^1$H NMR (CDCl3, 300 MHz) δ 2.01 (s, 3H), 2.15 (s, 3H), 5.22 (s, 1H), 7.21–7.49 (m, 5H). 11.58 (brs, 1H); $^{13}$C NMR (CDCl3, 300 MHz) δ 20.1, 30.5, 100.1, 128.7, 130.0, 132.4, 140.5, 161.7, 190.3; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.40; H, 7.45; N, 7.90

**4-(4-Chloro-phenylamino)-pent-3-en-2-one (3b):** (White solid); mp 64 ◦C; IR (cm−1) 3342, 3022, 1625, 1598, 1523, 1299, 1221, 1036, 777; $^1$H NMR (CDCl3, 300 MHz) δ 2.03 (s, 3H), 2.14 (s, 3H), 5.25 (s, 1H,), 7.19 (d, 2H), 7.35 (d, 2H), 11.41 (brs, 1H); $^{13}$C NMR (CDCl3, 300 MHz) δ 19.8,30.0, 99.0, 117.4, 125.3, 128.4, 137.4, 160.7, 190.4; Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; Cl, 16.91; N, 6.68. Found: C, 63.05; H, 5.76; Cl, 16.89; N, 6.70.

**3-Benylamino-but-2-enoic acid ethyl ester (3c):** (Colorless liquid); IR (cm$^{-1}$) 3299, 3041, 2997, 1654, 1621, 1464, 1291, 1254, 1188, 1098, 768; $^1$H NMR (CDCl3, 300 MHz) δ 1.77 (t, 3H), 2.09 (s, 3H), 5.11 (q, 2H), 5.35 (d, 2H), 5.74 (s, 1H), 7.71–8.08 (m, 5H), 10.47 (brs, 1H); $^{13}$C NMR (CDCl3, 300 MHz) δ 17.2, 20.1, 50.7, 61.5, 89.4, 127.5, 129.0, 130.4, 140.2, 162.9, 175.4; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.18; H, 7.77; N, 6.40.

**3-(4-Methoxy-phenylamino)-but-2-enoic acid ethyl ester (3d):** (Yellow oil); IR (cm$^{-1}$) 3291, 2966, 2857, 1678, 1629 1535, 1298, 1178, 1054, 786; $^1$H NMR (CDCl3, 300 MHz) δ 1.88 (t, 3H), 2.05 (s, 3H,), 3.98 (s, 3H,), 4.21 (q, 2H), 4.77 (s, 1H), 6.97 (d, 2H), 7.24 (d, 2H), 11.25 (brs, 1H); $^{13}$C NMR (CDCl3, 300 MHz) δ 16.5, 19.1, 59.1, 61.3, 89.4, 118.5, 128.6, 134.7, 160.4, 163.8, 178.1; Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.33; H, 7.27; N, 5.92.

**4-Phenylamino-pent-3-en-2-one (3h)**: (White solid); mp 50 ◦C; IR (cm$^{-1}$) 3481, 3045, 3075, 1621, 1554, 1533, 1288, 1198, 1024, 965, 747, 701; $^1$H NMR (CDCl3, 300 MHz) δ 2.02 (s, 3H), 2.17 (s, 3H), 5.23 (s, 1H), 7.45–7.87 (m, 5H). 11.48 (brs, 1H); $^{13}$C NMR (CDCl3, 300 MHz) δ 20.1, 29.4, 99.7, 126.2, 127.6, 130.8, 141.3, 161.5, 200.4; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.41; H, 7.50; N, 7.97.

**4-Benzylamino-pent-3-en-2-one (3i):** (Yellow viscous oil); IR (cm$^{-1}$) 3436, 3045, 1674, 1541, 1365, 1288, 1035, 775; $^1$H NMR (CDCl3, 300 MHz) δ 1.99 (s, 3H), 2.08 (s, 3H), 4.65 (d, 2H), 5.11 (s, 1H), 7.41–7.65 (m, 5H), 11.26 (brs. 1H); $^{13}$C NMR (CDCl3, 300 MHz) δ 19.8, 28.8, 50.0, 97.6, 127.9, 129.5, 131.9, 140.7, 166.2, 199.7; Anal. Calcd For $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.19; H, 7.97; N, 7.39.

## RESULTS AND DISCUSSION

In order to optimize the reaction conditions for the synthesis of β-enaminones under mild and solvent-free conditions, we chose the model reaction involving ethylacetoacete and benzyl amine at ambient temperature condition. In order to find out the best reaction conditions, a set of experiments was performed using varying amount of 3-nitrophenylboronic acid as a catalyst. The results of our optimization study are presented in Table 1. In the absence of the catalyst (entry 1) the reaction gave very low yield of the product which clearly indicates the need

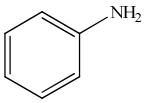
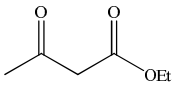
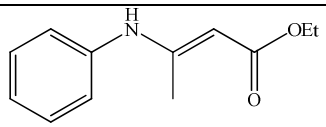
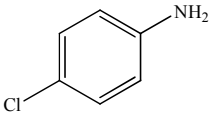
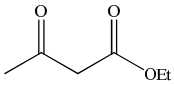
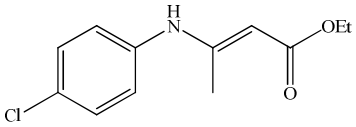
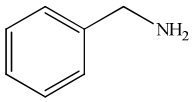
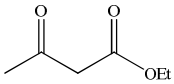
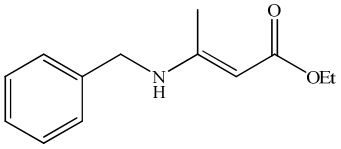
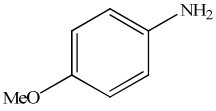
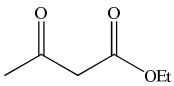
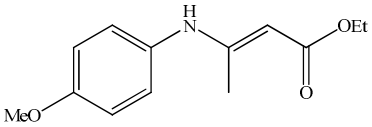
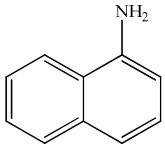
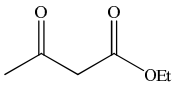
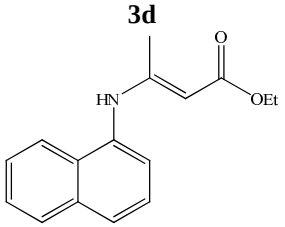
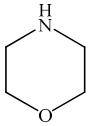
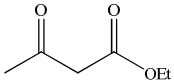
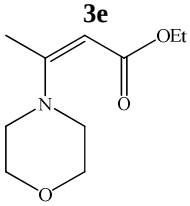
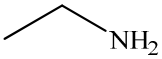
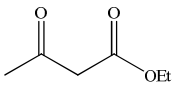
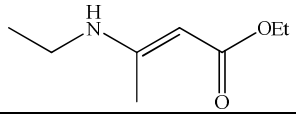
for catalyst for the success of the reaction. The catalytic loading as low as 1 mol % (entry **2**) was effective to proceed the enamination, however, 2.5 mol % of catalyst was found to be optimal to obtain the highest yield of the enamination product. Interestingly, the enamination could be completed within less than an hour when the amount of the catalyst was doubled (Table 1, entry **5**) giving almost similar yield of the desired product. But, in view of our objective to develop relatively cheap and environmentally benign protocol, we preferred the former conditions as an optimal one. Thus the best reaction condition for the present reaction were 1 mmol of β-keto ester, 1 mmol of amine in the presence of 2.5 mol % of 3-nitrophenylboronic acid under solvent-free conditions for 2 h at ambient temperature .

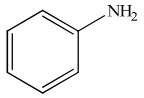
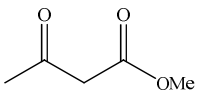
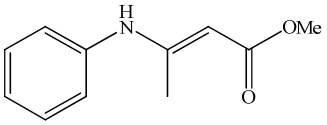
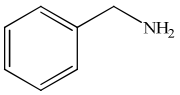
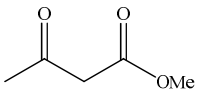
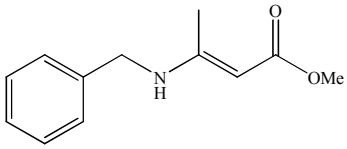
**Table 1. Optimization of the reaction conditions[a]**

| Entry | NPBA (mol %) | Time (h) | Yield of **3** (%)[b] |
|---|---|---|---|
| 1 | None | 2 | 24 |
| 2 | 1.0 | 2 | 41 |
| 3 | 2.0 | 2 | 78 |
| 4 | 2.5 | 2 | 96 |
| 5 | 5.0 | 5 | 94 |

*[a]Conditions: Amine (1 mmol), ethyl acetoacetate (1 mmol), 3-nitrophenylboronic acid (2.5 mol%) at ambient temperature. [b]Isolated Yield.*

**Table 2. Synthesis of β -enaminones catalyzed by 3-nitrophenylboronic acid[a]**

| Entry | Amine | β -keto ester | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  **3a** | 87 |
| 2 |  |  |  **3b** | 90 |
| 3 |  |  |  **3c** | 92 |
| 4 |  |  |  **3d** | 85 |
| 5 |  |  |  **3e** | 83 |
| 6 |  |  |  **3f** | 92 |
| 7 |  |  |  | 95 |

| | | | | |
|---|---|---|---|---|
| 8 |  |  | **3g**  | 85 |
| 9 |  |  | **3h**  **3i** | 91 |

[a]*Conditions: Ethyl acetoacetate (1 mmol), amine (1 mmol), and 3-nitrophenylboronic acid (2.5 mol%) at ambient temperature.* [b]*Isolated Yield.*

With good result being obtained in the reactions with benzyl amine, next in order to gauge the generality and scope of the present method, the structurally diverse amines such as aliphatic and cyclic, primary as well as secondary amines were subjected to enamination with ethyl acetoacetate using our optimized reaction conditions (**Scheme 1**). As show in our results (Table 2), in all the examples studied the reaction proceeded smoothly to afford the corresponding β-enaminones in high yields under present reaction conditions. The reactions were performed under solvent-free conditions and reached to completion within 2 h. at ambient temperature. The present reaction represents the true catalytic process for the synthesis of a wide variety of β-enaminones as a very small amount (2.5 mol %) of the catalyst was found to be effective to obtain the high yields of the products within short reaction times.

## CONCLUSION

The mild and solvent-free conditions, low catalytic requirement, simplicity and high yields of the products coupled with the use of environmentally benign catalyst makes the present methodology as an attractive synthetic protocols for the synthesis of a wide variety of β- enaminones at ambient temperature.

**Acknowledgement**
We acknowledge Dr. P. L. More and Dr. W. N. Jadhav, Dnyanopasak College, Parbhani for his constant encouragement and Financial support for this work by DST-SERC, New Delhi (SR/FT/CS-023/2008) is highly appreciated.

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