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Methylboronic Acid: A Mild, Green and Recyclable Organocatalyst for Transesterification of β-Keto Esters

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ABSTRACT

An environmentally benign, mild and selective protocol for the transesterification of β-ketoesters using methylboronic acid (Me-B(OH)$_2$, as a recyclable organoatalyst has been developed.

Keywords: Methylboronic acid; Transesterification; Recyclable

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INTRODUCTION

β-Ketoesters constitute highly important building blocks as they can be readily transferred into variety of heterocycles such as, 3,4–dihydropyrimidine-2(*1H*)-ones, 1,4–dihydropyridines, pyrrole furan, thiophenes etc [1-4]. They can also be transformed into chiral building blocks by chemical and enzymatic transformation and functions as a tool to perform chain-extension reactions [5]. The various β-ketoesters can be synthesized by protic [6] and Lewis acids [7] as well as alkaline catalysis [8]. In recent years, plethora of reagents for transesterification of β-ketoesters are have been reported which include diphenylammonium triflate [9], $B(OH)_3$ [10], NBS [11], yttria– zirconia [12], zeolites [13], Mo–ZrO_2 [14], Zinc [15], montmorillonite K-10 [16], B_2O_3/ZrO_2 [17] , Mg–Al–O–*t*-Bu hydrotalcite [18], $NaIO_4$/KIO_4/anhy. $CaCl_2$ [19] and nano CuFe2O4 [20]. In addition 4-DMAP [21, 22], AgOTf [23], distannoxane [24], ytterbium (III) triflate [25], Zeolite Ferrierite (H-FER) and solid superacid (sulphated SnO_2) [26], Kaolinitic clay [27] etc have also been tested for effecting this transformation.

As compared to heterogeneous catalyst, despite of the advantages such as low cost, robust nature and nontoxicity, organocatalysts have been very rarely explored for effecting transesterification process.

In 2006, Tale *et al.*[28] reported for the first time that mild, green and highly efficient 3-nitrobenzene boronic acid catalyzed efficient transesterification of various β-keto esters with a variety of alcohols as well as thiols, (scheme-2.5). The method is highly selective towards β-keto esters and provides good to high yields of the corresponding transesterified products. However, the 3-nitrobenzene boronic acid used here cannot be recycled which in turn makes the process little uneconomical.

In continuation of interest in exploring boronic acid as catalysts in organic synthesis, we report here that methylboronic acid was found to be mild, green and recyclable organocatalyst for effecting the transesterification of various β-Keto esters with diverse alcohols.

EXPERIMENTAL SECTION

Materials and techniques

The methyl boronic acid, β-ketoesters, alcohols etc. were purchased from Johnson-Matthy chemical Ltd. The solvents and other chemicals were purchased from S.D. Fine Chemical, India. All the solvents were redistilled before use. The progress of the reaction was monitored by thin layer chromatography using silica gel coated plates.

The petroleum ether used refers to the fraction 60-80 ^{0}C. The ^{1}HNMR and ^{13}CNMR spectra were recorded on Brucker Avance II 400 NMR spectrometer using tetramethylsilane as internal standard. Chemical shifts are reported in ppm (δ) relative to the solvent peak. The products were purified by column chromatography. The products were purified by column chromatography. The purity of the product was checked by TLC and ^{1}HNMR/ ^{13}C NMR spectral analyses.

General procedure

General procedure for the transesterification of β-keto esters:

To a 25 ml round bottomed flask charged with β-keto ester (1 mmol), appropriate alcohol (1mmol) and methyl boronic acid (5 mol %, 3mg) in 10 ml of toluene and equipped with Dean-Stark apparatus was added 4 A^0 molecular sieves (200 mg). The resulting mixture was heated at reflux while stirring for 10h with removal of ethanol from toluene-ethanol azeotrope. After completion of the reaction (TLC), the mixture was filtered off, solvent concentrated under vacuum and residue was taken up in sodium hydroxide solution (10ml), and extracted with ethyl acetate (3*10 ml). The combined organic extract was washed with water, dried over anhy. sodium sulphate and concentrated under vaccum to get crude product which was then purified by column chromatography (Eluent, petroleum ether : ethyl acetate 9:1) to obtain analytically pure transesterified product.

Procedure for recycling and reuse of the catalyst:

After completion of the reaction, the reaction mixture was filtered off and cooled to room temperature upon which methylboronic acids was precipitated out gradually. The supernant was decanted and addition of small portion of toluene and decantation repeated several times. Then the requisite amount of β-ketoester, appropriate alcohol, 4 A^o molecular sieves and toluene were added to the flask a second run was carried out. The above procedure was exactly followed for subsequent run. No significant drop in the yield was observed upto 3rd run.

Analytical data

1) decyl 3-oxobutanoate (3a)

^{1}H NMR (400 M Hz, $CDCl_3$): δ 0.74, (t, 3H), 1.19-1.28 (m, 14H), 1.53-1.60 (m, 2H), 2.24 (s, 2H), 3.37 (s, 2H), 4.02 (q, 2H)

^{13}C NMR (400 M Hz, $CDCl_3$): δ 14.0, 22.6, 25.8, 28.4, 29.1, 29.2, 29.4, 30.0, 31.8, 50.1, 65.5, 89.76, 167.1, 200.5

2) 4-methoxybenzyl 3-oxobutanoate (3c)

^{1}H NMR (400 M Hz, $CDCl_3$): δ 2.23 (s, 3H), 3.46 (s, 2H), 3.80 (s, 3H), 5.10 (d, 2H), 6.87 (dt, 2H), 7.28 (d, 2H).

^{13}C NMR (400 M Hz, $CDCl_3$): δ 30.1, 50.1, 55.3, 67.0, 114.0, 127.7, 130.2, 159.8, 167.0, 200.4

3) Benzyl 3-oxobutanoate (3b)

^{1}H NMR (400 M Hz, $CDCl_3$): δ 2.25 (s, 3H), 3.49 (s, 2H), 5.17 (d, 2H), 7.32-7.39 (m, 5H).

^{13}C NMR (400 M Hz, $CDCl_3$): δ 30.1, 50.0, 67.1, 128.4, 128.5, 128.6, 135.2, 166.9, 200.3

4) Benzhydryl 3-oxobutanoate (3d)

^{1}H NMR (400 M Hz, $CDCl_3$): δ 2.19 (s, 3H), 3.51 (s, 2H), 6.92 (s, 1H), 7.21-7.32 (m, 5H), 7.33-7.37 (m, 5H)

^{13}C NMR (400 M Hz, $CDCl_3$): δ 30.1, 50.3, 89.8, 127.5, 128.1, 128.5, 139.5, 166.1, 200.2

5) Cinnamyl 3-oxobutanoate (3i)

^{1}H NMR (400 M Hz, $CDCl_3$): δ 2.28 (s, 3H), 3.50 (s, 2H), 4.79 (q, 2H), 6.24-6.31 (m, 1H), 6.65 (d, 1H), 7.26-7.28 (m, 1H), 7.30-7.34 (m, 2H), 7.38 (q, 2H)

6) 2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-10,13-dimethyl-17-(6-methylheptan-2-yl)-1H-cyclopenta [a]phenanthren-3-yl 3-oxobutanoate (3f)

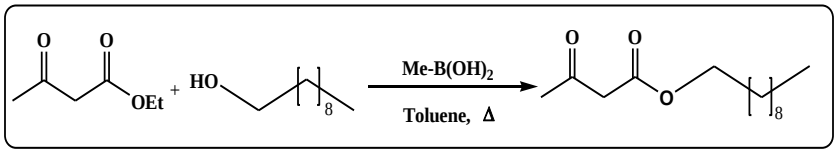
^{1}H NMR (400 M Hz, $CDCl_3$): δ 0.67 (s, 3H), 0.85 (d, 6H), 0.87 (d, 3H), 0.90-0.98 (m, 1H), 1.01 (s, 5H), 1.10-1.23 (m, 7H), 1.24-1.42 (m, 4H), 1.43-1.62 (m, 7H), 1.69 (s, 1H), 1.82-1.89 (m, 3H), 1.94 (s, 1H), 1.98-2.02 (m, 2H), 2.26 (s, 3H), 2.32 (d, 2H), 3.42 (s, 2H)

^{13}H NMR (400 M Hz, $CDCl_3$): 11.8, 18.7, 19.3, 21.0, 22.5, 22.8, 23.8, 24.2, 27.6, 28.0, 28.2, 30.0, 31.8, 31.9, 35.7, 36.1, 36.5, 36.9, 37.9, 39.5, 39.7, 42.3, 56.1, 56.6, 75.1, 122.9, 139.4, 166.5, 200.7

7) 3,5-bis(4-iodobenzyloxy)benzyl 3-oxobutanoate (3g)
^{1}H NMR (400 M Hz, $CDCl_3$): δ 2.25 (s, 3H) 3.50 (s, 2H), 5.14 (s, 4H), 6.54 (t, 1H), 6.56 (t, 2H), 7.00 (d, 4H), 7.53 (d, 2H), 7.69(tt, 4H)
8) Cinnamyl 3-oxo-3-phenylpropanoate (3h)
^{1}H NMR (400 M Hz, $CDCl_3$): δ 4.05 (s, 2H), 4.81-4.82 (m, 2H), 6.21-6.28 (m, 1H), 6.61 (d, 1H), 7.27-7.36 (m, 5H), 7.37-7.49 (m, 4H), 7.57-7.61 (m, 1H)

RESULTS AND DISCUSSION

In order to find out the optimum reaction conditions for methlyboronic acid catalyzed transesterification, the transesterification of ethyl acetoacetate with decanol in toluene (Dean stark extracter) was considered as model reaction, scheme-1. A series of experiments were carried out to search for optimal amount of catalyst for the smooth proceeding of the reaction. The results are summarized in table-1.



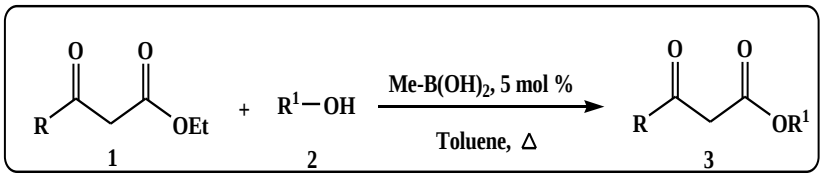
Scheme-1

Table 1: **Catalytic study for transesterification of β-keto ester catalyzed by methylboronic acid[a]**

Entry	Cat mol %	Time (h)	Yield (%)[b]
1	None	20	25
2	2	10	34
3	5	10	70
4	5	10	86[c]

[a]Reaction conditions; β-keto ester (1.0 equiv.), decanol (1.0 equiv.), and methyl boronic acid in toluene (10 ml), heated at reflux with stirring in Dean–Stark apparatius. [b] Isolated yields by column chromatography. [c] In the presence of 4 A^o molecular sieves.

As can be seen from our results, in the absence of catalyst the reaction was very sluggish and low yield was obtained despite of continuing the reaction for 20 h (table-1, entry-1). However, use of catalytic amount of methylboronic acid (table-1, entry-2) was found to promote the reaction within short reaction time albeit in moderate yield. We found that increasing the catalyst loading from 2 to 5 mol % increased the yield of a transesterified product to a good yield (table-1, entry-3). Finally, the use of 4 A^o molecular sieves was found to be advantageous as under these conditions yield increases considerably (table-1, entry-4). Thus the best results were obtained by using 5 mol % of the catalyst and in presence of molecular sieves. Having, good results being obtained in the reaction with decanol, in order to gauge scope and generality of the reaction, the transesterification of different β-keto esters with a wide range of alcohols were performed, (scheme-2.). Results are summarized in table-2.

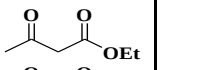
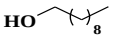
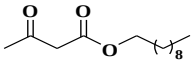
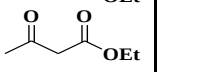
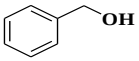
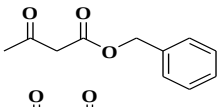
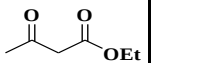
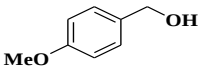
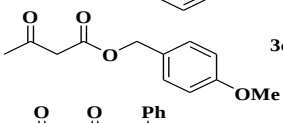
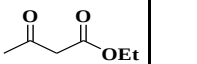
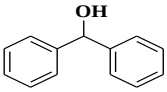
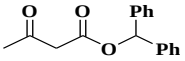
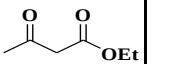
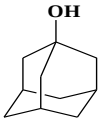
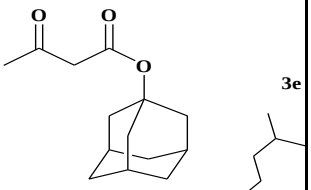
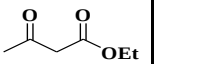
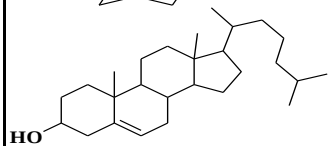
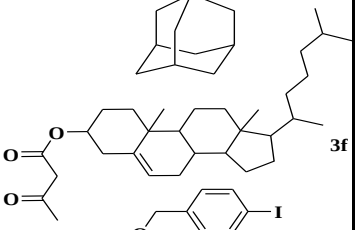
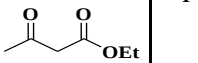
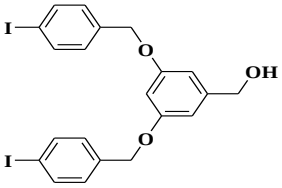
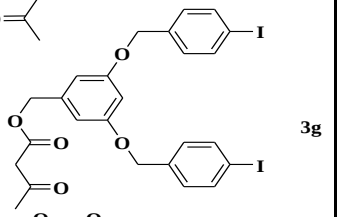
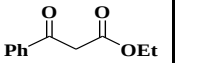
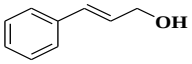
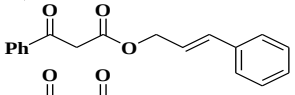
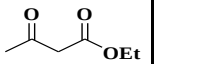
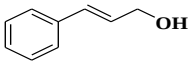
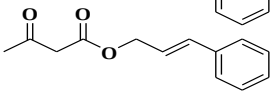
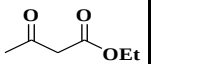
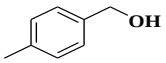
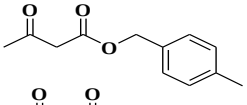
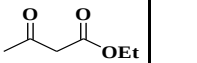
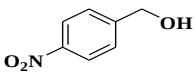
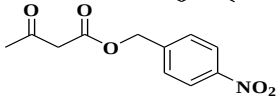


Scheme-2

As shown in table-2, alcohols such as primary, secondary, teritiary and benzylic alcohols reacted efficiently to afford the corresponding transesterified product in high yields. The reaction was found to be sensitive to the electronic effect of substituent on benzylic alcohols. The benzylic alcohols bearing electron releasing substituent shown higher reactivity (table-2, entries-3 & 10) than their electron deficient counterpart, (table-2., entries-11). More importantly, the transesterification with α, β-unsaturated alcohols such as cinnamyl alcohol also proceeded smoothly to give good yield of the transesterified product (table-2, entries- 8, 9). It is to be noted that transesterification of such a substrate is otherwise difficult due to facile decarboxylative rearrangement of the resulting product.
Interestingly, we also tested first time the dendritic alcohol such as [3,5-bis(*p*-iodobenzyloxy)]benzyl alcohol synthesized by Freche't approach in the present reaction, (table-2, entry-7). Thus, the novel β–keto esters bearing 1st

generation Freche't type dendron was obtained in good yield by this transesterification process. It's worth mentioning here that this novel β–keto ester could prove itself as highly useful building block for the synthesis of various heterocycles such 3,4-dihydropyrimidine-2(1*H*)-ones, 1,4-dihydropyridines, pyrrole furan etc. possessing dendritic unit. Not only electron rich benzylic alcohol but electron deficient one such as 4-nitrobenzyl alcohol also found to be suitable substrate in the present transesterifications process.

Table 2: Transesterification of β-keto esters with various alcohols catalysed by methyl boronic acid[a]

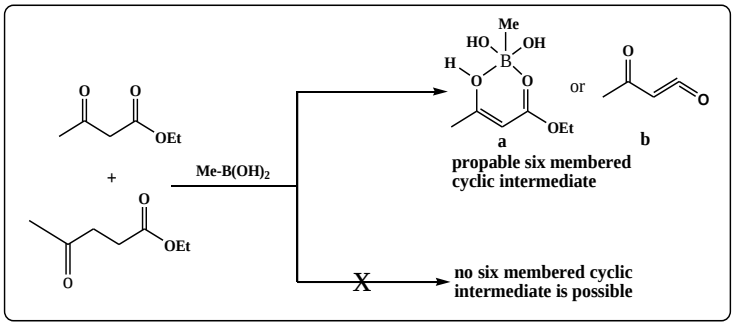
Entry	b-Keto ester	Alcohol	Product		Yield(%)[b]
1				3a	86
2				3b	75
3				3c	81
4				3d	73
5				3e	76
6				3f	62
7				3g	55
8				3h	63
9				3i	81
10				3j	78
11				3k	69

[a]Reaction conditions; β-keto ester (1.0 equiv.), alcohol (1.0 equiv.), Methyl boronic acid (5 mol %) and in presence of 4 A^{o} molecular sieves (200 mg) in reflux toluene (10 ml) in Dean–Stark apparatius for 10 h. [b]isolated yields by column chromatography

Having explored the scope of the reaction with different alcohols, next the scope of the reaction was also explored with different β-keto esters. Our results clearly indicate that the present reaction is not only applicable to aliphatic esters as well as aromatic ester reacted efficiently. For example, the reaction of ethyl 3-oxo-3-phenylpropanoate with cinnamyl alcohol afforded the cinnamyl 3-oxo-3-phenylpropanoate in good yield, (table-2, entries-8) using these

conditions. These both types of esters reacted with a wide variety of alcohols under present reaction conditions. This can be considered to be the significant advantage of this method as the transesterification of aromatic β-keto esters in protic acid catalysed reaction reported to give lower yields of the products.

In order to check whether the present reaction conditions could be adopted for the transesterification of other keto esters such as α-keto esters, γ-keto esters and normal esters three different experiments were carried out. We found that only β-keto esters reacted effectively and other esters failed completely under these reaction conditions. Thus, the most striking feature of the present methods is that the reaction is specific to β-keto esters only as the other esters such as α-keto esters, γ-keto esters and normal esters failed to react under these conditions. We believe that the probable reason for this difference in the reactivity between β-keto esters and other esters is the activation of the former through the co-ordination of boron with two oxygen atoms through six membered transition state **a** which is not possible in other esters. However the possibility of formation of acylketene intermediate, b as proposed by Lawrie and Cambell [29] cannot be ruled out at this stage, scheme-3.



Scheme-3

Thus the present reaction was found to be general as structurally diverse alcohols as well as β-keto esters reacted smoothly under present reaction conditions to give moderate to high yields of the corresponding transesterified products. Interestingly, the reaction was found to be specific toward the transesterification of β-keto esters. In view of one of the important aspects of catalysis, recycliblity issue, we thought its worthwhile to explored the possibility of recycling and reuse of present catalyst. After deep investigation during recyclability study, we found that the catalyst can be recycled and reused up to 3 runs without significant loss in the yield (Table 3). The catalyst can be recycled simple by cooling the mixture to room temperature, filtration followed by successive washing with toluene and decantation.

Table 3: Recycling study of the catalyst[a]

Entry	Run	Yield (%)[b]
1	1st	86
2	2nd	85
3	3rd	83

[a]Reaction conditons: ethylacetoacetate (1 mmol), decanol (1 mmol), methyl boronic acid (5 mol %) in presence of 4 A° molecular sieves (200 mg) in toluene (10 ml) under reflux with stirring in Dean–Stark apparatius for 10 h. [b] isolated yields by column chromatography.

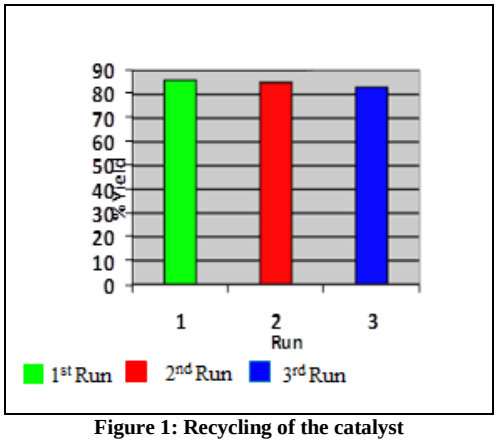


Figure 1: Recycling of the catalyst

CONCLUSION

The methodology developed here is mild, general and highly selective towards β-keto esters and provides good to high yields of the corresponding the diverse β-keto esters. The catalyst, methylboronic acid is commercially available, green and recyclable catalyst and is employed here for the first time. Its worth mentioning here that for the first time the novel dendritic alcohol such as Frechet type 1st generation dendron, G1OH has been tested as alcohol component in this reaction.

In conclusion, in the present work we have demonstrated for the first time the potential of novel methylboronic acid as a catalyst to develop an efficient, general, selective and envinormentally benign protocol for transesterification of β-keto esters.

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