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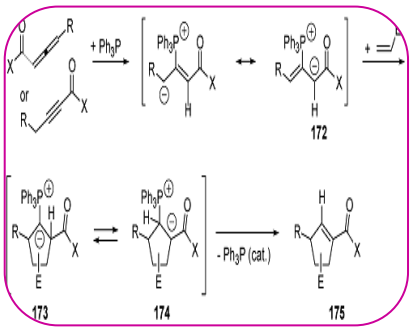
BENZOIC ACIDAS AN ORGANOCATALYST FOR THE TRANSESTERIFICATION OF B-KETO ESTER



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ABSTRACT:-

Benzoic acid have been proved to be efficient organocatalysts for transesterification of β-keto esters with various aromatic and hetero aromatic alcohols in toluene media, the transesterified product was obtained in moderate to high yields. Simple reaction conditions and inexpensive catalysts are important features of this method.

KEY WORDS: *Benzoic acid, aromatic alcohols.*

INTRODUCTION:

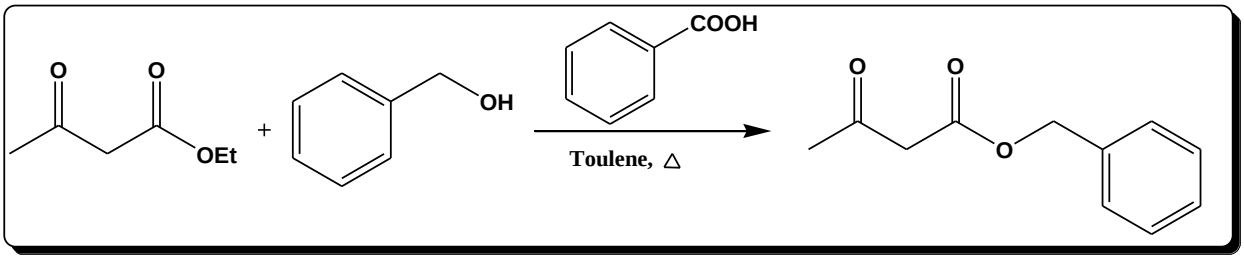
β-Ketoestersare important constitute of crucial building blocks since they are readily transfered into different types of heterocycles like 1,4–dihydropyridines, pyrrole furan, thiophenes, 3,4–dihydropyrimidine-2(*1H*)-ones etc. They can also be transformed into chiral building blocks by chemical transformation and functions as a tool to perform chain-extension reactions.[1] The various β-ketoesters can be synthesized by protic[2] and Lewis acids[3] as well as alkaline catalysis.[4]different types of reagents for transesterification of β-ketoesters are Diphenylammonium triflate,[5] B(OH)[6] NBS,[7] yttria–zirconia[8], zeolites[9], Mo–ZrO_2[10], Zinc[11], montmorillonite K-10[12], B_2O_3/ZrO_2[13], $NaIO_4/KIO_4$/anhy. $CaCl_2$,[14] and nano $CuFe_2O_4$[15], 4-DMAP[16] etc.

In the recent period, reactions catalyzed by metal-free organic molecules i.e. organocatalysis have become a very interesting and important area of research. Although organocatalysis generally requires a high quantity of catalyst and longer reaction time, compared with reactions carried out by catalysts of metal complexes, organocatalysts show many important advantages including their more stability towards moisture and oxygen, their ease of preparation, low toxicity and cheap.[17] All of these advantages are attractive towards the production of pharmaceutical intermediates. Since the rediscovery of organocatalysis at new millennium an exponential number of papers on this subject appeared over the years.[18] It generated several excellent reviews and books where various aspects of this field have been dissected.[19] Professor Pavel Kocovsky pointed out in 2006 that while the words 'asymmetric' and 'organocatalysis' were closely linked in the minds of the many scientists working in this field, chiral compounds are not the only valuable ones which can be conveniently prepared employing this methodology. The well-known attractive aspects of organocatalysis such as environmentally friendly conditions (no need for anhydrous conditions or of transition metals) without any doubt which can apply also to synthesis of achiral molecules. In a recent essay, List roots the origin of amino catalysis in the pioneering studies of Emil Knoevenagel in the 19th century. In these key papers and other earlier works, organocatalysis had just been seen as an effective methodology. Researchers are now starting to think organocatalytic when applying disconnecting strategies

to total syntheses. Some non-asymmetric organocatalytic reactions are so unexpected that they could not have been foreseen at the beginning of their relevant project. Most likely, many of these transformations are found by chance as 'spin-off' from some originally asymmetric projects. In several cases the achiral products are the undesired side products in an asymmetric transformation. As it has happened several times before, serendipity brought a significant advance in the field of science.

Though many catalyst being highly efficient, green organocatalysts and the high cost issues of many of them makes the organic processes uneconomical. With increasing economical concern and regularatory constraints faced by chemical and pharmaceutical industries, the development of further economical processes is highly desired in the field of organic chemical approaches. In this regard, the use of organocatalyst such as the benzoic acid which is relatively cheapand available in every common laboratory could provide viable alternative to the existing methods.

The present workdeal with development of novel, mild protocol for the transesterification of β-keto esters using the commercially available, inexpensive benzoic acid as Lewis acidic organocatalyst.



Scheme-1

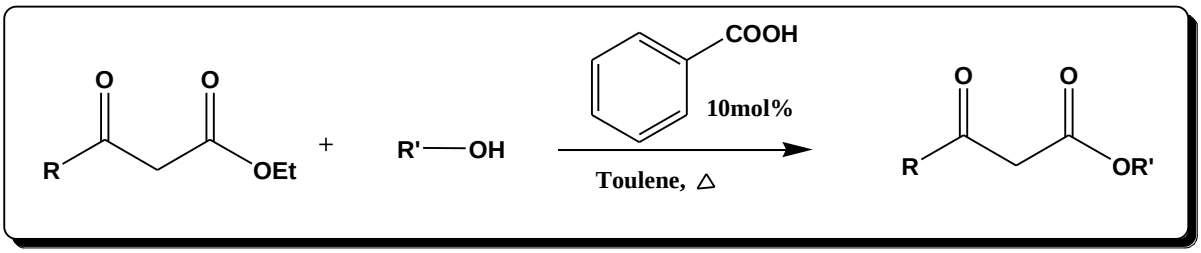
In order to find out the optimize reaction condition for benzoic acid catalyzedtransesterification, the transesterification of ethyl acetoacetate with benzyl alcohol in toluene (Dean stark extracter) was considered as model reaction (**scheme-1**). A series of experiments were carried out to find the optimal amount of catalystto set the best reaction condition. The results are shown in **table 1**.

Table -1: Catalytic study of benzoic acid for the transestification of β-ketoester[a]

Sr. no.	Catalyst mole%	Time (h)	Yield (%)[b]
1	00	18	20
2	02	15	25
3	05	15	45
4	**10**	**10**	**73**
5	10	15	75

[a]**reaction conditions:** β-keto ester (1.0 equiv), benzyl alcohol (1.0 equiv) and benzoic acid in toluene (10 ml) heated at reflux with stirring in Dean-Stark apparatus.[b]Isolated yield by column chromatography

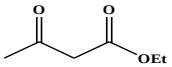
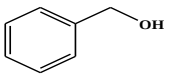
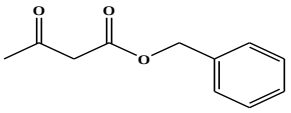
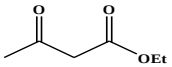
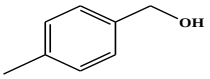
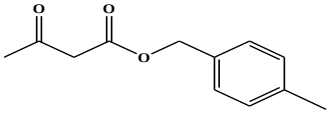
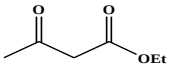
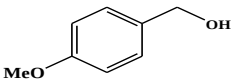
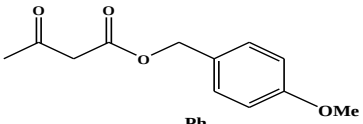
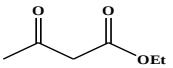
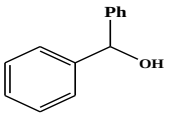
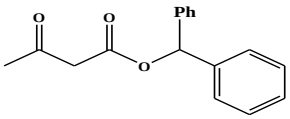
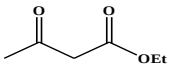
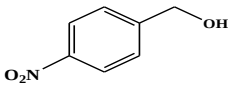
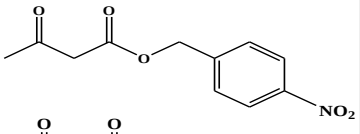
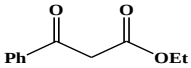
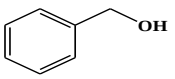
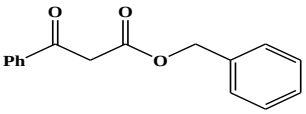
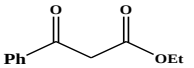
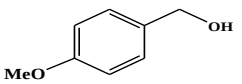
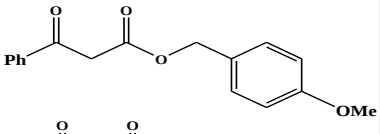
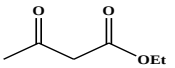
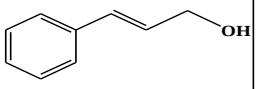
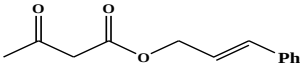
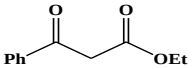
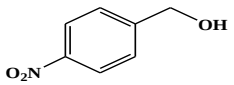
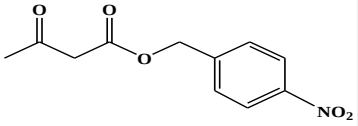
As can be seen from above table, in the absence of catalyst the reaction was very sluggish and low yield was obtained even though the reaction was continued for 18 h (table-2.1,entry-1). The use of catalytic amount of benzoic acid (table-1, entry-2) was found to be promote the reaction within short reaction time with low yield. We found that increasing the catalyst amount to 5 mol %, the moderate yield of transesterified product was obtained in 15h (table-1, entry-3). Finally, the use of 10mol% was found to be advantageous conditions to increase yield considerably more than 70% in 10h (table- 1, entry-4). Further, we tried to increase the reaction upto 15h using same quantity of catalyst but we found the marginal increase in the yield. Thus the best results were obtained by using 10 mol % of the catalyst in 10h.



Scheme-2

Having, good results being obtained in the reaction with benzyl alcohol in order to check the scope and generality of the reaction, the transesterification of different β-keto esters with a wide range of alcohols were performed (**scheme-2**).

Table-2 Benzoic acid catalysedtransesterification of β-keto ester with different alcohols[a]

Entry	b-keto ester	Alcohol	Product	Yield%[b]
01				75
02				78
03				82
04				72
05				60
06				70
07				78
08				68
09				58

[a]**reaction conditions:** β-keto ester (1.0 equiv), appropriate alcohol (1.0 equiv) and benzoic acid (10mol%) in toluene (10 ml) heated at reflux with stirring for 10h in Dean-Stark apparatus. [b]Isolated yield by column chromatography

As shown in **table-2**, alcohols such as primary, secondary and benzylic alcohols are reacted efficiently to give the corresponding transesterified product in high yields. The electronic donating groups on benzylic alcohols shown higher reactivity (table-2, entries-2, 3 & 7) than their electron deficient benzyl alcohol, (table-2, entries-5 &9). 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.

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 benzyl alcohols afforded in good yield, (table-2, entries-6 & 7) 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 is catalysed by benzoic acid reported.

The methodology developed here is mild, general and provides the diverse β-keto esters in good to high yields. The catalyst, benzoic acid is commercially available catalyst is employed here for the first time. In conclusion, in the present work we have demonstrated for the first time the potential of novel benzoic acid as a catalyst to develop an efficient, general and environmentally benign protocol for transesterification of β-keto esters.

MATERIALS AND METHODS

The benzoid acid, β-ketoesters, alcohols,solvents and other chemicals etc. were purchased from Bio Treasure India.All the solvents were redistilled before use. The progress of the reaction was monitored by thin layer chromatography. The petroleum ether used refers to the fraction 60-80 ^{0}C. The products were purified by column chromatography. The purity of the product was checked by TLC and representative^{1}HNMR/ ^{13}C NMR spectral data analyses were taken from our previous research work.

GENERAL PROCEDURE FOR THE TRANSESTERIFICATION OF B-KETO ESTERS

To a 25 ml round bottomed flask charged with β-keto ester (1 mmol), appropriate alcohol (1mmol) and benzoid acid (10 mol %) in 10 ml of toluene and equipped with Dean-Stark apparatus. 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 taken up in 10% sodium bicarbonate 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.

ANALYTICAL DATA

1) **benzyl 3-oxobutanoate : ^{1}H NMR (400 M Hz, CDCl3):** 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, CDCl3):** δ 30.1, 50.0, 67.1, 128.4, 128.5, 128.6, 135.2, 166.9, 200.3
2) **benzhydryl 3-oxobutanoate : ^{1}H NMR (400 M Hz, CDCl3):** 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, CDCl3):** δ 30.1, 50.3, 89.8, 127.5, 128.1, 128.5, 139.5, 166.1, 200.2

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REFERENCES:

1. (a) Demirbas, A. *Energy Convers. Manage.*,**2008**, *49*, 125–130; (b) Demirbas, A. *Energy Convers. Manage*., **2003**, *44*, 2093–2109; (c) Bala, B. K. *Energy, Educ., Sci. Technol.*, **2005**, *15*, 1–43; (d) Haas, M. J. *Fuel Process. Technol*., **2005**, *86*, 1087–1096; (e) Abreu, F. R.; Lima, D. G.; Ham´u, E. H.; Wolf, C.; Suarez, P. A.

Z. *J. Mol. Catal. A: Chem.*, **2004**, *209*, 29–33; (f) Brito, Y. C.; Ferreira, D. A.; Fragoso, D. M. de A.; Mendes, P. R.; De Oliveira, C. M. J.; Meneghetti, M. R.; Meneghetti, S. M. P. *Appl. Catal., A*, **2012**, 202–206; (g) Kawasaki, M.; Goto, M.; Kawabata, S.; Kodama, T.; Kometani, T. *Tetrahedron Lett.,* **1999**, *40*, 5223–5226.

2. (a) Rehberg, C. E.; Fisher, C. H. *J. Am. Chem. Soc.*, **1944**, *66*, 1203–1207; (b) Rehberg, C. E.; Faucette, W. A.; Fisher, C. H. *J. Am. Chem. Soc.*, **1944**, *66*, 1723–1724; (c) Rehberg, C. E. *Organic Synthesis, Wiley, New York*, **1955**, Collect. vol. *3*, p. 146; (d) Haken, J. K. *J. Appl. Chem.*, **1963**, *13*, 168.
3. (a) Yazawa, H.; Tanaka, K.; Kariyane, K. *Tetrahedron Lett.*,**1974**, *15*, 3995–3996; (b) Blossey, E. C.; Turner, L. M.; Neckers, D. C. *Tetrahedron Lett*., **1973**, *14*, 1823–1826; (c) Hoydonckx, H. E.; De Vos, D. E.; Chavan, S. A.; Jacobs, P. A. *Top. Catal.*,**2004**, *27*, 83–96; (d) Kumar, P. R.; Kumar, P. *Catal. Commun*.,**2007**, *8*, 1122–1125.
4. (a) Taber, D. F.; AmedioJr, C. J.; Patel, Y. K. *J. Org. Chem.*, **1985**, *50*, 3618–3619; (b) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *ChemInform*, **1991**, *22*, 275; (c) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, D.; Weidmann, B.; Zugger, M. *Synthesis*, **1982**, 138–141; (d) Kroszczy´nki, W.; Olszewska, E.; Sała´nski, P.; Jurczak, J. *Helv. Chim. Acta*, **2004**, *87*, 1488–1492.
5. Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett*.,**2000**, *41*, 5249–5252;
6. Kondaiah, G. C. M.; Reddy, L. A.; Babu, K. S.; Gurav, V. M.; Huge, K. G.; Bandichhor, R.; Reddy, P. P.; Bhattacharya, A.; Anand, R. A. *Tetrahedron Lett*., **2008**, *49*, 106–109.
7. Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Synlett*, **2001**, 1715–1718.
8. Kumar, P.; Pande, R. K. *Synlett*, **2000**, 251–253
9. Balaji, B. S.; Chanda, B. M. *Tetrahedron,* **1998**, *54*, 13237–13252.
10. Reddy, B.M.; Reddy, V.R.; Manohar, B. *Synth. Commun.* **1999,** *29*, 1235
11. Chavan, S. P.; Shivasankar, K.; Shivappa, R.; Kale, R. *Tetrahedron Lett*. **2002**, *34*, 5883.
12. Jin, T.; Zhang, S.; Li, T. *Green Chem.* **2002**, *4,* 32.
13. Madje, B. R.; Patil, P. T.; Shindalkar, S. S.; Benjamin, S. B.; Shingare, M. S.; Dongare, M. K. *Catalysis Commun.* **2004**, 353-357
14. Bandgar, B.P.; Hashmi, A.M.; Pandit, S. S. *J. Chinese Chem. Soc.,* **2005**, *52*, 1101-1104
15. Gohain, M.; Kumar, V.; Tonder, J. H.V.; Swart, H. C.; Ntwaeaborwa, O. M.; Bezuidenhoudt, B. C. B. *RSC Advances*, **2015**, *5*, 18972
16. (a) Gilbert, J. C.; Kelly, T. R. *J. Org. Chem.*, **1988**, *53*, 449– 450; (b) Taber, D. F.; Amedio Jr., J. C.; Patel, Y. K. *J. Org. Chem.*, **1985**, *50*, 3618–3619;
17. Emsley, J.; The Elements, 3rd ed., Oxford University Press, **1998**.
18. See, for examples: Pelter, A.; Smith, K.; Brown, H. C.; *Borane Reagents*, Academic Press, London, **1998**; Smith, K.; „Organoboron Chemistry". In *Organometallic in Synthesis*, ed. M.Schlosser, Wilet, Chinchester, **1994**.
19. a) Hall, D. G. Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine; Wiley-VCH: Weinheim, **2011**, and references cited therein; b) Hall, D. G. Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Second Edition) Wiley-VCH: Weinheim, **2011**, and references cited therein.; c) Guan, Y.; Zhang, Y. *Chem. Soc. Rev.*, **2013**, *42*, 8106; d) Cambre, J. N.; Sumerlin, B. S.; Polymer **2011**, 52, 4631. Hall, D.G. Structure, properties of Boronic acid derivatives overview of their reactions and applications; Wiley-VCH verlag GmbH & Co. **2011**, and references cited therein.