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$Al(H_2PO_4)_3$: An Efficient and Effective Solid Acid Catalyst for Transesterification of β-keto Esters Under Solvent Free Condition

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Abstract $Al(H_2PO_4)_3$ is an efficient, cheap and reusable heterogeneous catalyst for transesterification of β-ketoesters with a variety of alcohols in moderate to good yields within a short reaction time under solvent free condition.

Keywords β-keto esters · Alcohols · Transesterification · Solid catalyst · Catalytic synthetic protocol

The transesterification of β-keto esters is an important transformation in organic synthesis as they are precursors of many important chemical intermediates, agrochemicals, polymer as well as in pharmaceutical industries [1]. The transesterification strategy is also employed for preparing optically active compounds from β-ketoesters by reaction with chiral alcohols [2]. Conventionally, dimethylamino pyridine (DMAP) is used as a choice of reagent for transesterification of β-keto esters in good yields, but it suffers from the limitations such as toxicity, high price and requirement of large amount of catalyst [3]. Over the years several catalysts like distannoxane [4], triphenyl phosphine [5], zeolites [6], kaolinitic clay [7], Zn/I_2 [8], ceria–yttria based Lewis acid catalyst [9], Nb_2O_5 [10], 3-nitrobenzeneboronic acid [11] have been reported to accelerate the rate of transesterification of β-keto esters. Similarly some other heterogeneous catalysts such as S-SnO_2 [12], Amberlyst-15 [13], Envirocat EPZF^R [14], montmorillonite K-10 [15], B_2O_3/ZrO_2 [16] are also effective for the transesterification of β-ketoesters. Nevertheless, there is still an ample scope to search for an effective catalyst for transesterification as most of the methods suffer from drawbacks such as longer reaction time, tedious work-up procedure, harsh reaction conditions and expensive reagents.

Recently, there has been a considerable interest to develop catalysts for organic reactions by supporting inorganic reagents on inorganic materials having high surface area [17]. The nature of support has an important role in the catalytic activity mainly due to the intimate contact between the supported ions and the support surface. Moreover, the mechanical stability, ease of separation of catalyst from the reaction mixture and reusability are the added advantages of these solid catalysts.

We wish to report herein the transesterification of β-ketoesters with a wide range of alcohols by using 5 mol% of solid acid catalyst $Al(H_2PO_4)_3$ under solvent free condition within a very short reaction time (Scheme 1).

$Al(H_2PO_4)_3$ is a solid acid catalyst which is easy to prepare, stable, easily separable from the reaction mixture and recyclable which was prepared by literature procedure [18]. For optimization, the reaction of methyl acetoacetate with benzyl alcohol was carried out at various conditions and the results are summarized in Table 1. A blank reaction of methyl acetoacetate (5 mmol) and benzyl alcohol (5.5 mol) without using the catalyst was carried out which gave only 15% of the desired β-keto ester even after stirring for 24 h at room temperature. The same reaction in presence of $Al(H_2PO_4)_3$ (0.5 mol%) at room temperature (Table 1, entry c), gave 50% yield after 24 h. Next, we tried to improve the yield and time of the reaction by heating the reaction mixture at 80 °C, which was completed within 20 min with 92% yield (Scheme 2).

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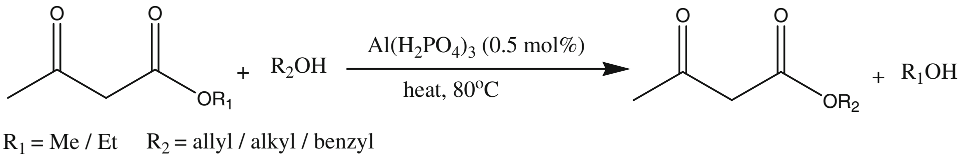
Scheme 1



Scheme 2

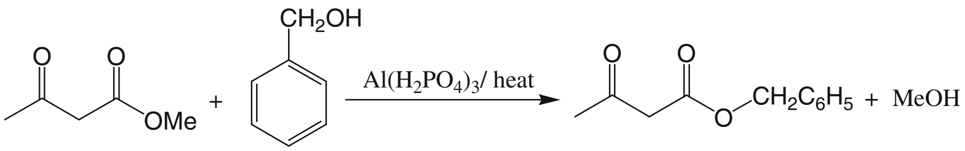


Table 1 The results of the reaction of methylacetoacetate with benzyl alcohol

Entry	Catalyst	Time/h [min]	% Yield^{a,b}
a	No catalyst/rt	24	15
b	Al_2O_3(5 mol%)/rt	24	35
c	$Al(H_2PO_4)_3$(0.5 mol%)/rt	24	50
d	$Al(H_2PO_4)_3$(0.5 mol%)/heat	[20]	92

[a] Isolated yields

[b] All the reactions were carried out in 5-mmol scale

[c] For reusability test, reaction was carried out in 50 mmol scales and the catalyst was recycled up to consecutive three more cycles without loss of its activity in 89, 85 and 80% yields respectively

In order to prove the generality of the reaction, Table 2 presents the results of transesterification of *β*-keto esters with wide range of structurally diverse alcohols with catalytic amount of $Al(H_2PO_4)_3$. As can be seen from the table, open chain, cyclic, benzylic, allylic alcohols reacted efficiently with *β*-keto esters to furnish products in good yields. Notably unsaturated alcohols (Table 2, entries 2a–2c) reacted smoothly with methyl acetoacetate in very good yield even though literature study highlights the difficulty in the transesterification of this substrate due to its successive decarboxylation and rearrangement [19]. Long chain transesterified products(Table 2, entries 3d−3e) mainly used as precursors in polymer industry were obtained in moderate to good yields. Similarly, menthol (Table 2, entry 2g) on treatment with methyl acetoacetate provided menthyl acetoacetate in 85% yield. Interestingly, ethyl cyclopentanone-2-carboxylate (Table 2, entry 1h), a sterically hindered substrate also reacted with menthol to furnish the desired product (Table 2, entry 3 h) without any difficulty. Remarkably, the transesterified product (Table 2, entry 3i) was also obtained by the reaction of sterically bulky cyclododecanol (Table 2, entry 2i) with methyl acetoacetate under similar reaction condition. Although benzyl alcohols are prone to form benzyl ethers in some of the reported conditions this alcohol (Table 2, entries 2j) underwent transesterification easily with the present catalyst. Moreover, methyl acetoacetate gave doubly transesterified products with various diols like 1,8-octane- and 1, 4-butyne diols (Table 2, entry 2n–2o), respectively. Though long chain aliphatic, cyclic and benzylic alcohols easily reacted with methyl acetoacetate, phenols and tertiary alcohols did not undergo the transesterification reaction even after prolonging it under similar reaction conditions. All the products were characterized by recording ^1H and ^{13}C NMR as well as by elemental analysis.[1]

The significance of the catalyst lies in its ease of preparation. Moreover the recovered catalyst can be reused after filtering from the reaction mixture and reactivating by heating at 200–220 °C for 30 min without any remarkable loss of activity as indicated in Table 3. The catalyst was reused upto three cycles for the reaction of methyl acetoacetate and benzyl alcohol.

The efficacy and versatility of the catalyst was further proved by comparing the reaction of methyl acetoacetate and cyclohexyl alcohol with other reported catalysts (Table 4).

The most salient feature about this reported procedure is that only the *β*-keto esters have undergone the transesterification reaction explicitly as compared to *α*-keto esters, *γ*-keto esters or normal esters which failed to react completely. The catalyst probably activates the *β*-keto esters to form an acyl ketene intermediate which is not feasible for the other esters as proposed by Campbell and Lawrie [20]. In order to further prove the reaction mechanism, we carried out another set of reaction between two different *β*-ketoesters as suggested by the referees. Equimolar amounts of methyl acetoacetate and ethyl benzoylacetate

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[1] Methyl acetoacetate (5 mmol), alcohol (5.5 mmol) and $Al(H_2PO_4)_3$ (0.03 mmol, 0.5 mol %) were placed in a 25 mL round bottom flask fitted with a condenser. The reaction mixture was heated at 80°C and the progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled and filtered. The residue was washed with chloroform and the filtrate was evaporated under pressure. The crude product was purified by passing through a silica gel column using (hexane:ethyl acetate::9:1) as eluent to furnish the pure product. The solid catalyst was recovered, reheated and reused.

Table 2 Transestrification of *β*-ketoesters using catalytic amount of $Al(H_2PO_4)_3$

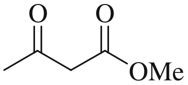
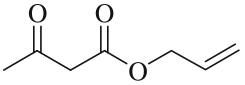
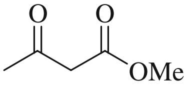
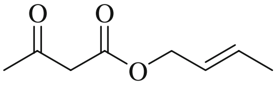
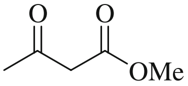
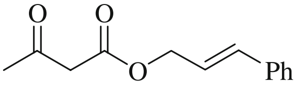
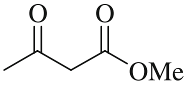
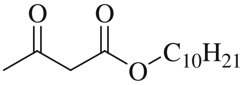
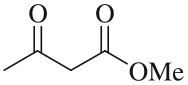
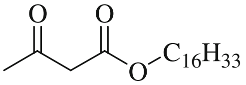
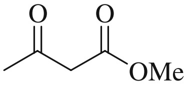
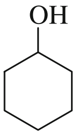
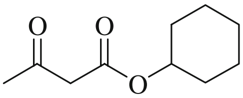
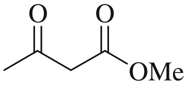
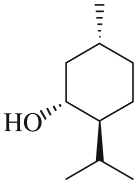
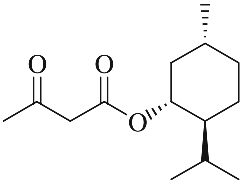
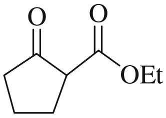
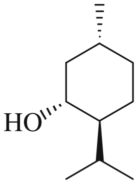
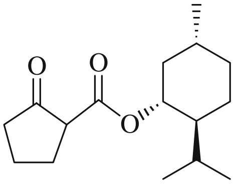
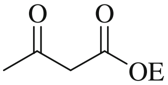
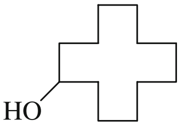
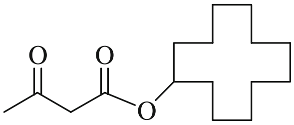
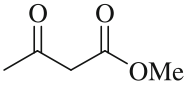
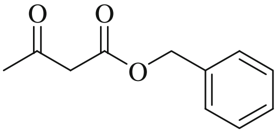
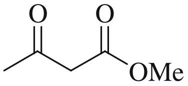
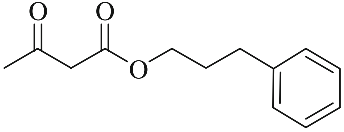
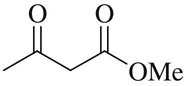
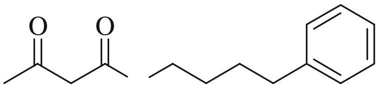
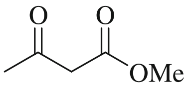
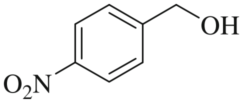
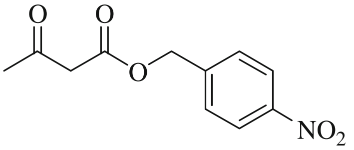
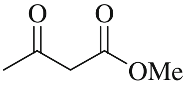
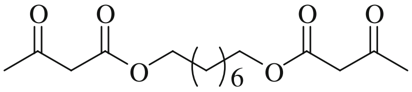
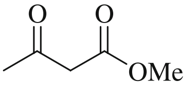
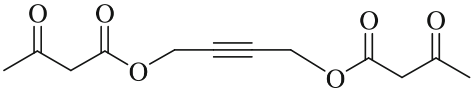
Entry	β-Ketoester (**1**)	Alcohol (**2**)	Time/min	Product (**3**)[a]	%Yield[b]
a		CH_2=CH-CH_2OH	10		93
b		CH_3CH=$CHCH_2OH$	15		90
c		PhCH=$CHCH_2OH$	20		91
d		$CH_3(CH_2)_8CH_2OH$	20		89
e		$CH_3(CH_2)_{14}CH_2OH$	25		82
f			20		94
g			20		85
h			20		89
i			15		88
j		$PhCH_2OH$	20		92
k		$PhCH_2CH_2CH_2OH$	15		88
l		$PhCH_2(CH_2)_2CH_2OH$	20		90

Table 2 continued

Entry	β-Ketoester (**1**)	Alcohol (**2**)	Time/min	Product (**3**)[a]	%Yield[b]
m			20		91
n		$HOCH_2(CH_2)_6CH_2OH$	30		81
o		$HOCH_2C{\equiv}CCH_2OH$	30		70

[a] Products were characterized by IR, ^1H NMR and ^{13}C NMR spectra as well as elemental analysis

[b] Isolated yield

Allyl 3-oxobutanoate (Table 2, entry3a): Colourless viscous oil; IR (neat, cm^{-1}) ν: 1747, 1716, 1660. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 3.48 (s, 2H), 4.63 (d, J = 5.6 Hz, 2H), 5.25 (dd, J = 0.8 Hz, J = 10.4 Hz, 1H), 5.33 (dd, J = 1.2 Hz, J = 16.8 Hz, 1H), 5.85−5.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.12, 50.00, 65.73, 118.53, 131.27, 166.41, 199.91. Anal. Calcd. for $C_7H_{10}O_3$: C 59.15, H 7.09; found: C 59.22, H, 7.01

Cyclododecyl 3-oxobutanoate (Table 2, entry3i): Viscous oil; IR (neat, cm^{-1}) ν: 1736, 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.33 (bs, 9H), 1.38 (bs, 9H), 1.48–1.56 (m, 2H), 1.68–1.76 (m, 2H), 2.26 (s, 3H), 3.41 (s, 2H), 5.04–5.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.88, 21.01, 23.19, 23.26, 23.36, 23.86, 24.06, 24.25, 28.98, 29.22, 30.14, 32.47, 50.44, 73.53, 166.50, 200.44. Anal. Calcd. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.43, H 10.40

1,8-Octanyl Bis(3-oxobutanoate) (Table 2, entry 3n): Colourless viscous oil; IR (neat, cm^{-1}) ν: 1747, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (bs, 8H), 1.62–1.65 (m, 4H), 2.27 (s, 6H), 3.45 (s, 4H), 4.12 (t, J = 6.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.70 (2C), 28.40 (2C), 29.00 (2C), 30.17 (2C), 50.06 (2C), 65.36 (2C), 166.88 (2C), 200.28 (2C). Anal. Calcd. for $C_{16}H_{26}O_6$: C 61.13, H, 8.34; found: C 60.97, H 8.28

Table 3 The recycling of 0.5 mol% of catalyst $Al(H_2PO_4)_3$

Entry	Time (min)	Yield (%)[a]
1	20	92
2	30	89
3	45	85
4	60	80

[a] For reusability test, reaction was carried out in 50 mmol scales

Table 4 Comparison of $Al(H_2PO_4)_3$ with other reported catalyst

Entry	Catalyst	Time (h) [min]	Isolated yield (%)	References
1	Ceria–ytteria	8	95	9
2	B_2O_3/ZrO_2	3	85	16
3	3-nitrobenzeneboronic acid	10	92	11
4	Zn/I_2	5	60	8
5	$Al(H_2PO_4)_3$	[20]	92	–

was allowed to react by heating at 80 °C for 20 min. As anticipated, the alcohol fragments of both the β-ketoesters got interchanged, even in absence of alcohols from external source, to give methyl benzoylacetate and ethyl acetoacetate respectively. This observation thereby strengthens the fact that the reaction invariably proceeds through the ketene intermediate. We believe that the catalyst recycled as the reaction took place in heterogeneous medium on the solid surface of the catalyst. After the completion of the reaction, the product dissociates from the catalytic site and goes into the solution phase. The reaction is further continued by the approach of another new substrate molecule to the catalytic site, followed by the release of the product into the solution phase.

In conclusion we have devised a simple and efficient synthetic protocol for transesterification of β-keto esters using a cheap and reusable heterogeneous catalyst. Although literature enumerates a number of procedures for the transesterification of β-keto esters, the simplicity, lesser reaction time, environmental acceptability and inexpensiveness of our catalyst makes it a practical alternative. We believe this protocol will be a new addition in the field of modern organic synthesis.

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M.K.Chaudhari for his catalyst.The authors are also grateful to the Director, IIT Guwahati for providing general research facility to carry out the work. Finally the authors thank the reviewers for their valuable suggestions.

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