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Efficient *trans*-acetoacylation mediated by ytterbium(III) triflate as a catalyst under solvent-free condition

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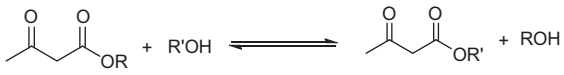
ABSTRACT

A simple and efficient *trans*-acetoacylation method for the synthesis of β-keto ester derivatives has been described using ytterbium(III) triflate as a new catalyst under solvent-free condition. This method was found to be efficient and convenient for the synthesis of a wide variety of β-keto ester derivatives.

trans-Acetoacylation is an exchange process of alkoxy moiety of ester with an alcohol to form new esters (Scheme 1). The *trans*-acetoacylation reaction has received considerable attention, essentially for the synthesis of polymers, drugs and biologically active compounds.[1] β-Keto esters have also been used as a building block for the synthesis of several complex natural products[2] due to their electrophilic and nucleophilic nature. Synthesis of β-keto esters can be achieved from the reaction between diketene with readily available alcohol or by condensation between the two esters in a basic medium (Claisen condensation). Diketenes as such are very reactive, corrosive and very difficult to handle. Commercially also, a few β-keto esters are available. However, by using *trans*-acetoacylation it is very easy to synthesize a wide variety of β-keto esters, which are not available commercially.



Scheme 1.

trans-Acetoacylation is an equilibrium process, and it is very difficult to maintain equilibrium towards the desired product. To overcome this problem, several methods are reported in the literature, and synthesis of β-keto esters could be achieved by using acidic and basic catalysts,[3] such as Bronsted base,[4] DMAP,[5] Zeolites,[6] super acid,[7] montmorillonite,[8] zinc/I_2,[9] amberlyst-15,[10] Nb_2O_5[11] and NBS.[12] *tert*-Butylacetoacetate could also be converted easily into its corresponding esters in catalyst-free condition,[13] which was essentially due to the presence of a better leaving group. Moreover, great deal of attention has been paid towards *trans*-acetoacylation of lower homologue to higher homologue.

Ytterbium(III) triflate has been utilized as a mild Lewis-acid catalyst in various organic transformations.[14–16] In continuation of our studies on the synthesis of various bioactive compounds,[17] we have examined the ytterbium(III) triflate for the *trans*-acetoacylation of β-keto esters. The reported methods suffer from one or other drawbacks, such as longer reaction times, harsh reaction conditions, difficulty in isolation of products, usage of halo and carcinogenic solvents and modest yields of the desired β-keto esters. Therefore, these drawbacks prompted us to examine a new catalyst that might be suitable for *trans*-acetoacylation. Herein, we report ytterbium(III) triflate as a versatile catalyst for the *trans*-acetoacylation reaction.

In order to standardize the reaction conditions, a model reaction was carried out by making use of methyl acetoacetate, ethanol and ytterbium(III) triflate (Table 1, entry 1). It was observed that methyl acetoacetate, alcohol and $Yb(OTf)_3$ in 1:1:0.3 ratios in solvent-free condition gave better results. The standardized reaction conditions were further extended to a wide range of functionalized alcohols.

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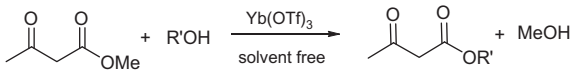
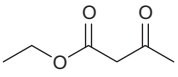
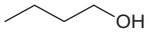
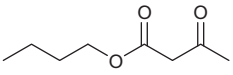
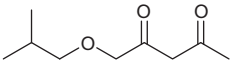
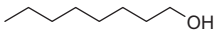
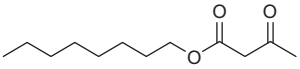
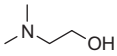
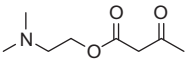
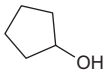
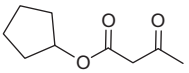
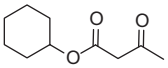
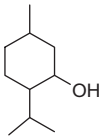
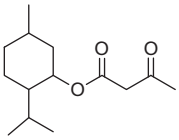
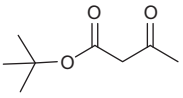
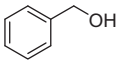
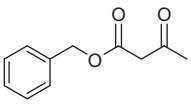
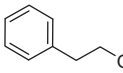
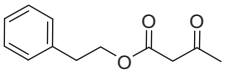
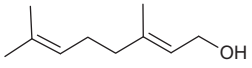
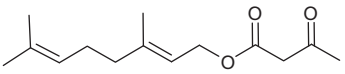
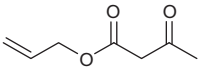
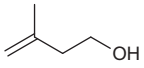
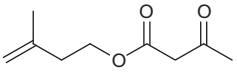
Table 1
trans-Acetoacylation reaction catalysed ytterbium(III) triflate[a]



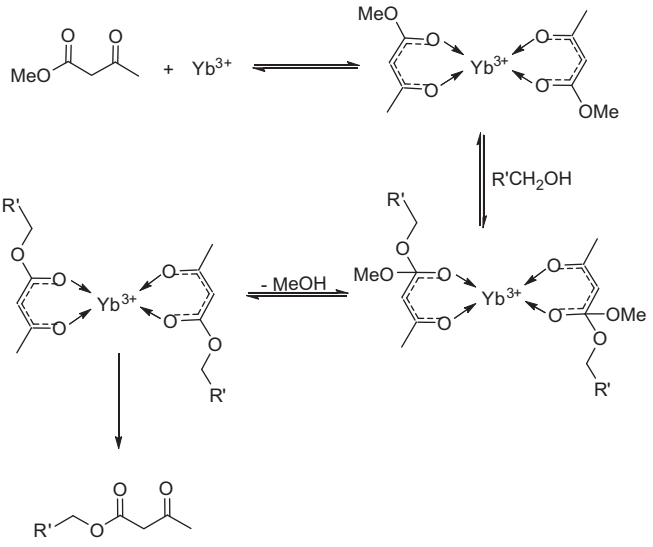
S. No.	Alcohol (R′)	β-Ketoester	Time (h)	% Yield[b]
1			3	94
2			3	94[9]
3			3	90[9]
4			3	92[9]
5			3	90
6			3	89
7			3	91[9]
8			3	85[9]
9			4.5	65[7]
10			3	90[9]
11			3	87
12			4	80
13			3	80[9]
14			4	82

[a] *Reaction conditions:* methyl acetoacetate (1 equiv.), alcohol (1 equiv.) and $Yb(OTf)_3$ (0.3 equiv.) under reflux, solvent free conditions.[18]
[b] Isolated yields separated by column chromatography.

A noteworthy merit of the present protocol is that all the primary alcohols (Table 1, entries 1–5, and 10–14), secondary alcohols (Table 1, entries 6–8), and tertiary alcohols (Table 1, entry 9) underwent *trans*-acetoacylation easily and rapidly to the corresponding β-keto esters. Modest yield was obtained in case of tertiary alcohol, due to steric hindrance. Results are summarized in Table 1.

On the basis of the above observations and literature reports, a plausible mechanism for the *trans*-acetoacylation with $Yb(OTf)_3$ is depicted in Scheme 2. In the first step, methylacetoacetate reacts with Yb(III) to form a complex of methylacetoacetate, and the desired product was obtained by the attack of alcohol on Yb(III) complex of methylacetoacetate. The equilibrium is thus shifted due to the loss of relatively volatile methyl alcohol at 110 °C from the reaction mixture and results in the formation of the desired product.

In summary, we have described a new and highly efficient procedure for the *trans*-acetoacylation by using $Yb(OTf)_3$ as a mild catalyst under solvent-free conditions. The advantages of this method are simple operation, mild reaction conditions and simple work-up.



Scheme 2.

Acknowledgments

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18. *Typical experimental procedure*: A homogeneous mixture of methyl acetoacetate (1 mmol) and alcohol (1 mmol) was taken in a round bottomed flask attached to reflux and a distillation condenser to remove methanol. A catalytic amount of $Yb(OTf)_3$ (0.3 mmol) was added and the reaction was heated at 110 °C (oil bath) with constant stirring under solvent-free condition for a certain period of time as required, and the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and the crude β-ketoester was separated by column chromatography using light petroleum ether and ethylacetate (80:20) to afford the pure desired product.
2-(dimethylamino) ethyl 3-oxobutanoate (**5**): IR (ν_{Max}): 854, 1175, 1719, 1748, 2861. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.289 (s, 9H), 2.569–2.598 (t, J = 5.6 Hz, 2H), 3.495 (s, 2H), 4.233–4.261 (t, J = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ = 29.706, 45.383, 45.608, 50.059, 58.444, 69.195, 167.212, 200.517. ESI-MS: m/z = 174.21 [M+1].
Cyclopentyl 3-oxobutanoate (**6**): IR (ν_{Max}): 803, 968, 1151, 1323, 1718, 1740, 2874, 2966. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.590–1.603 (2H, m), 1.613–1.626 (5H, m), 1.842–1.856 (2H, m), 2.260 (s, 3H), 3.411 (s, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.603, 29.933, 32.592, 50.320, 78.171, 166.809, 200.575. ESI-MS: m/z = 193.03 [M+23].
Phenethyl 3-oxobutanoate (**11**): IR (ν_{Max}): 701, 749, 995, 1031, 1150, 1316, 1717, 1743, 2960. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.199 (s, 3H), 2.965–2.982 (t, J = 6.8 Hz, 2H), 3.423 (s, 2H), 4.353–4.370 (t, J = 6.8 Hz, 2H), 7.307 (s, 5H). ^{13}C NMR ($CDCl_3$) δ = 29.858, 34.808, 49.883, 65.576, 126.541, 128.426, 128.736, 137.336, 166.865, 200.618. ESI-MS: m/z = 229.03 [M+23].
3,7-dimethylocta-2,6-dienyl 3-oxobutanoate (**12**): IR (ν_{Max}): 802, 958, 1150, 1233, 1314, 1378, 1446, 1648, 1719, 2929, 2968. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.602 (s, 3H), 1.682 (s, 3H), 1.769 (s, 3H), 2.119–2.144 (m, 4H), 2.263 (s, 3H), 3.438 (s, 2H), 4.612–4.643 (d, 2H), 5.088–5.072 (t, 1H), 5.335–5.370 (t, 1H). ^{13}C NMR ($CDCl_3$) δ = 17.601, 23.433, 25.622, 26.578, 30.022, 32.143, 50.102, 61.950, 118.557, 132.209, 143.228, 167.068, 200.433. ESI-MS: m/z = 261.09 [M+23].
3-methylbut-3-enyl 3-oxobutanoate (**14**): IR (ν_{Max}): 803, 895, 1040, 1151, 1317, 1451, 1719, 1744, 2970, 3079. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.755 (s, 3H), 2.264 (s, 3H), 2.346–2.381 (t, J = 6.8 Hz, 2H), 3.445 (s, 2H), 4.248–4.282 (t, J = 6.8 Hz, 2H), 4.739–4.814 (d/d, 1H). ^{13}C NMR ($CDCl_3$) δ = 22.191, 29.889, 36.398, 49.891, 63.288, 112.303, 141.164, 166.898, 200.232. ESI-MS: m/z = 193.06 [M+23].