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An efficient synthesis of β-ketoesters via transesterification and its application in Biginelli reaction under solvent-free, catalyst-free conditions

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ABSTRACT

A simple and efficient transesterification process for the synthesis of β-ketoester derivatives has been achieved by the reaction of methyl β-ketoester with higher alcohols at 110 °C under solvent-free, catalyst-free conditions and its application in synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones C-5 ester derivatives via Biginelli reaction has been described.

The recent focus on the development of sustainable chemical process has provided an emerging task to those who applied chemistry in industry and academic research. The construction of chemical compounds or protocols by avoiding relatively volatile toxic solvents and hazardous catalysts is the need in the present scenario for green synthesis.[1,2] Besides, it has been observed that the catalyst employed protocols are not always environmentally benign, and because of this several environmental solid mass pollutants often result during the process of waste disposal. These limitations prompted us to investigate the efficiency, viability and feasibility of solvent and catalyst-free reactions under modified experimental conditions toward the development of a greener protocol for the synthesis of diversified and functionalized cascade molecules.

In the current existence, transesterification transformation has received considerable attention and emerged as the most significant protocol in organic synthesis (Scheme 1).[3] Transesterification was one of the easiest procedures for the synthesis of β-ketoesters, which are not available commercially. β-Ketoesters serves as an authoritative synthon which were used in the synthesis of polymers, drugs, and biologically active compounds.[4] Besides this they are also used as building blocks in the synthesis of complex natural products.[5] β-Ketoesters have also proved to be a superior synthon essentially because of the presence of both electrophilic as well as nucleophilic centers. Transesterification reaction is also more advantageous than the Claisen condensation or the reaction of diketene with alcohols for the synthesis of β-ketoesters. Diketenes were very difficult to handle due to corrosive and very reactive nature.

tert-Butyl β-ketoester readily underwent transesterification transformation with alcohol to form the corresponding β-ketoester in the presence of toluene/xylene as solvent under catalyst-free condition[6] due to the presence of better leaving group and this protocol was only restricted to *tert*-butyl β-ketoester. Toluene was found to be the best solvent in comparison to other solvents. However, it was not found to be environmental friendly. Transesterification is an equilibrium driven process and it can be controlled by acidic and basic catalysts[7] in hydrocarbon solvents or usage of excess of one of the precursor to get quantitative yield.

Literature survey revealed that, most of the reported methods were developed either by the use of catalyst[8] or solvents.[9] However, in spite of their potential utility, most of these reported methods experienced from various disadvantages such as drastic reaction conditions, modest yields, requires special experimental

Scheme 1. General transesterification transformation.

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apparatus and the use of catalysts which are expensive, toxic, and air sensitive. To the best of our knowledge, there are no reports for transesterification of alcohol under solvent-free and catalyst-free conditions using methyl β-ketoester as the acetoacetylating agent.

In continuation of our work on new synthetic methodologies for the synthesis of various bioactive compounds[10] there was a need to synthesize various functionalized β-ketoesters. Recently, we have developed a protocol for the transesterification of alcohols by using ytterbium(III)triflate as catalyst under solvent-free conditions.[11] With an objective to develop a greener protocol of transesterification, the reaction (Scheme 1) was carried out under solvent-free and catalyst-free conditions to obtain a number of β-ketoesters by the simple and commonly used method of transesterification from readily available methyl β-ketoester. Herein, we report a realistic method for the synthesis of β-ketoester using methyl β-ketoester with different functionalized alcohols under solvent-free and catalyst-free conditions at 110 °C.

With the intention of optimize the reaction conditions, we initiated our investigation on transesterification of methyl β-ketoester with cyclohexanol as a model substrate. The cyclohexanol β-ketoester was obtained in moderate yield, when methyl β-ketoester was reacted with an equilmolar amount of cyclohexanol (1:1) in the absence of solvent and catalyst after 3 h at 110 °C. The methyl β-ketoester was completely converted into cyclohexanol analogue, which was obtained in 85% yield (Table 1, entry 6). It also revealed that the reaction proceeds under solvent-free and catalyst-free conditions, when methyl β-ketoester and cyclohexanol were used in a mole ratio of 1:1.5 (Fig. 1).

The applicability of optimized reaction conditions were further extended to the synthesis of a more complex β-ketoester with a wide range of structurally diverse and functionalized alcohols. As expected, the rate of this transformation also depends on steric hindrance and all the results are appended in Table 1. The salient features of this methodology are as follows, (i) methyl β-ketoester is successfully transformed into synthetically useful higher homologue of esters; even bulkier alcohols could be used for transesterification (Table 1, entry 7), (ii) the synthesis of long chain esters which can be used as precursors in the polymer industry (Table 1, entry 4), (iii) the special features of this protocol is that unsaturated alcohols (Table 1, Entries 13–15) smoothly underwent transesterification affording unsaturated esters in high yields.

β-Ketoester is one of the precursors, out of the three building blocks in the Biginelli reaction[13] to synthesize the 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) which occupied a prestigious position in medicinal chemistry due to their pharmacological and biological activities such as calcium channel blockers, mitotic kinesine inhibitor, adrenergic receptor antagonist, antibacterial, and antiviral activities.[14,15] The β-ketoester can be varied to the largest extent by the synthesis of non-commercial β-ketoester via transesterification as mentioned above to achieve diversity at the C-5 position of DHPMs.

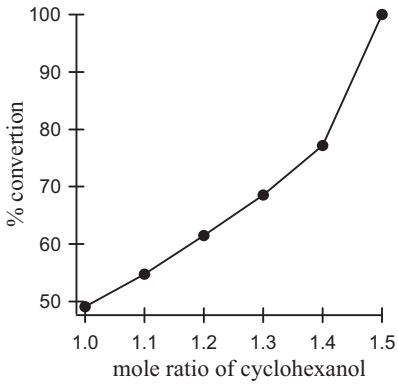
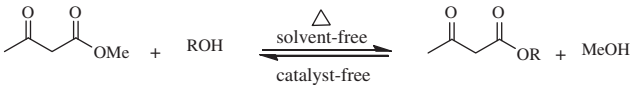
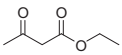
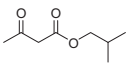
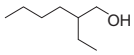
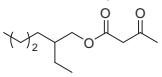
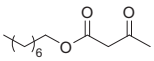
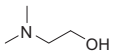
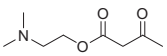
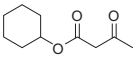
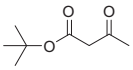
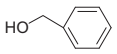
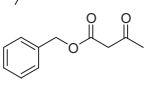
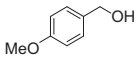
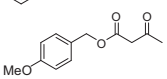
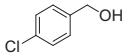
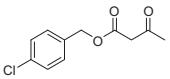
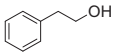
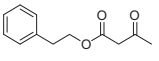
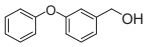
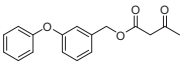
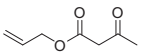
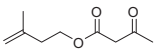
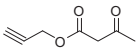


Figure 1. Comparison of various mole ratios of cyclohexanol with methly β-ketoester in transesterification (GC yields).

Table 1
Transesterification of methyl β-ketoester using various alcohols[a,16]



Entry	ROH	Time (h)	Product	Yield[b] (%)
1		3		92[11]
2		3		90[11]
3		3		85
4		3		85[11]
5		3		90[11]
6		3		85[11]
7		5.5		60[11]
8		3.5		88[11]
9		3		90
10		4		85
11		3		83[11]
12		4		80
13		3		80[11]
14		4		76[11]
15		3		75[12]

[a] Reaction and conditions: methyl β-ketoester (1.0 equiv), and alcohol (1.5 equiv) at 110 °C under solvent- and catalyst-free conditions.
[b] Isolated yields.

Recently, we have reported a Biginelli reaction[10a] for the construction of dihydropyrimidinones/thiones. The same procedure was employed to Biginelli reaction under solvent-free and catalyst-free conditions by using various types of β-ketoesters which were synthesized via transesterification transformation with constant arylaldehyde. From these experiments, we found that tolerance of various β-ketoesters bearing diverse functionality underwent the reaction smoothly with *p*-methoxy benzaldehyde and urea to afford the corresponding dihydropyrimidinone C-5 ester derivatives in excellent yields and all the results are appended in Table 2.

On the basis of the above observations and the literature reports, a plausible reaction pathway for the formation of dihydropyrimidinone C-5 ester derivatives is depicted in Scheme 2. Methyl β-ketoester is easily converted into reactive acetylketene intermediate[6] by the loss of relatively volatile methyl alcohol at 110 °C followed by the nucleophilic attack of the alcohol to form