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Ytterbium Triflate Catalyzed Michael Additions of β -Ketoesters in Water

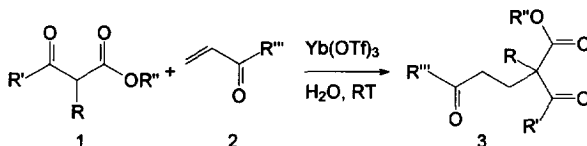
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Abstract: Michael addition of various β -ketoesters towards enones and α,β -unsaturated aldehydes resulted in a quantitative conversion to the corresponding 1,4-adducts by performing the reactions in water in the presence of ytterbium triflate as a water-tolerant Lewis acid.

In recent years there has been growing recognition that water is an attractive medium for many organic reactions,¹ in particular when one considers the need to develop environmentally acceptable chemical processes. Water as a solvent was not frequently used until recently for several reasons such as insolubility of the reactants or the reactivity of reagents towards water, although it is by far the most common liquid in our environment. Lanthanide triflates have been shown to be effective water-tolerant Lewis acids in several carbon-carbon bond forming reactions such as aldol and Diels-Alder reactions, and in some cases the presence of water even improves their activity.² The use of water as a solvent in the Michael addition of 1,3-diketones has been reported occasionally.³ In contrast the Michael addition of β -ketoesters does not give appreciable reaction rates in water under neutral conditions. Furthermore, the scope of the Michael reaction in water has, to our knowledge, not been investigated. Our interest in catalytic carbon-carbon bond formation, in particular using conjugate addition reactions^{4,5} prompted us to investigate the use of lanthanide triflates in the catalytic Michael addition of β -ketoesters towards α,β -unsaturated compounds in water as the solvent.

It is known that Michael additions of β -ketoesters and dialkyl malonates can readily be catalyzed by various mild Lewis acids under non-aqueous conditions.⁶ We now report the highly efficient catalytic Michael addition of β -ketoesters in water in the presence of catalytic amounts of ytterbium triflate as Lewis acid (Scheme 1).⁷ When the 1,4-addition of β -ketoesters **1** to methyl vinyl ketone **2** ($R''' = \text{CH}_3$) was performed in water in the presence of 10 mol% of $\text{Yb}(\text{OTf})_3$ at room temperature, quantitative yields of adducts **3** were found.



Scheme 1

Table 1 Michael Addition of β -Ketoesters and Methyl Vinyl Ketone

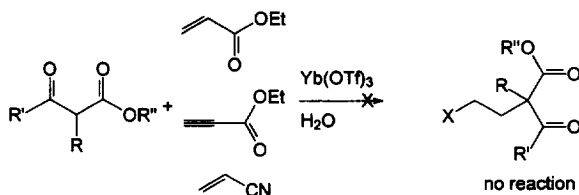
Entry	Michael donor	conditions ^a	Michael adduct	Reaction time (d) ^b
1		suspension		3
2		homogeneous		5
3		suspension		5
4		homogeneous		5 (mono-Michael adduct)
5		suspension		5
6		homogeneous		5

a: Catalyst Yb(OTf)₃, solvent H₂O

b: Isolated Yields >98 %

Results obtained using several Michael donors are listed in Table I. First we investigated the scope of the reaction by changing the structure of the Michael donor with methyl vinyl ketone (MVK) as the acceptor. Both cyclic and acyclic β -ketoesters were used in this reaction and in all cases the desired Michael adducts were isolated in quantitative yield when the reaction was performed in water in the presence of 10 mol% of ytterbium triflate. Stirring the reaction mixture at room temperature for a period of three to five days was necessary to reach high conversion but control experiments showed that in the absence of catalyst even after fourteen days only about forty percent of the starting material was converted into the desired product. In sharp contrast, little or no reaction was observed when the same ytterbium triflate catalyzed 1,4-addition was performed in organic solvents like THF, dioxane or methylene chloride. It is interesting to notice that although the β -ketoesters in some cases do not give homogeneous solutions, the solubility does not influence the conversion of the Michael donor. For example, in entry 2 the reaction mixture is completely homogeneous,

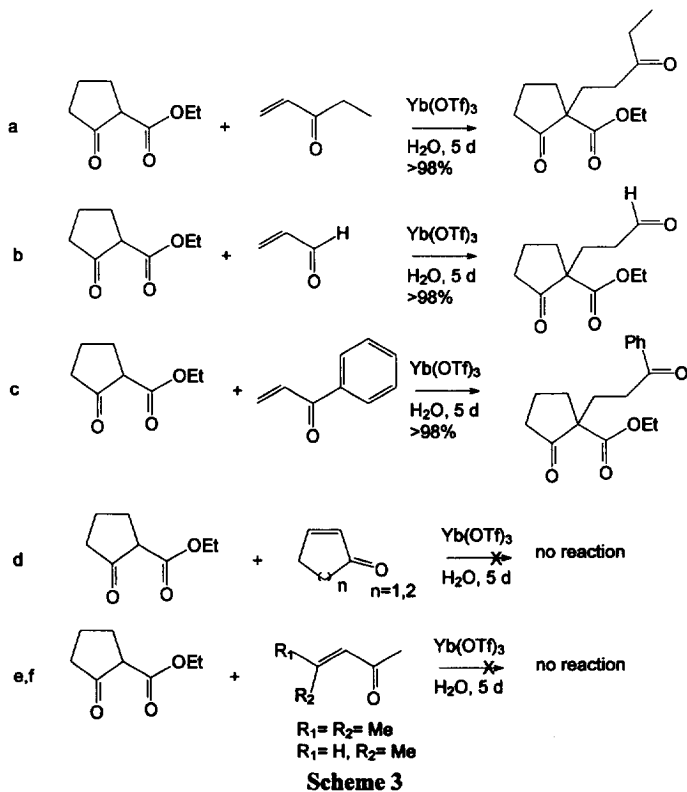
whereas for entry 1 the Michael donor is suspended in the aqueous solution. Furthermore it should be emphasized that highly pure products were obtained using a simple procedure and in most cases no further purification was needed.⁷ In all cases, hydrolysis of the ester functionality was not observed. Furthermore yields are generally higher than the yields reported for 1,4-additions catalyzed by other mild Lewis acids in common organic solvents.⁶



Scheme 2

Next, various Michael acceptors were tested. However when acrylonitrile, ethyl acrylate or ethyl propiolate were used, only starting materials were recovered in all cases using several β -ketoesters, even after prolonged reaction times (Scheme 2). From the Michael acceptors bearing alternative electron withdrawing groups only acrolein did give the desired 1,4-addition product, again in quantitative yield (a typical example is given in Scheme 3, reaction b).

Since the addition of the various β -ketoesters did proceed smoothly with MVK, a number of α,β -unsaturated enones bearing different substituents at the β or the α' position were tested (Scheme 3).



Scheme 3

From this scheme it can be seen that effective 1,4-addition under aqueous conditions only proceeds with β -unsubstituted enones. Although we did not observe decreased reactivity for the α,β -unsaturated enones with a substituent at the α' -position, substituents at the β -position are not allowed. The reduced reactivity for β -substituted α,β -unsaturated enones is not unexpected, since these compounds often require more drastic conditions in conjugate addition reactions.⁸

In conclusion, we have succeeded in performing the ytterbium triflate catalyzed Michael addition of β -ketoesters towards β -unsubstituted α,β -unsaturated enones and enals under very mild conditions. When water is used as the solvent in the presence of a catalytic amount of ytterbium triflate, the chemical yield and the purity of the product could be considerably improved compared to traditional methods using organic solvents. Further studies on the scope and limitations of this reaction and, in addition, the catalytic enantioselective Michael additions in water, are currently under investigation.

Acknowledgement:

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Notes and References:

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7. In a typical procedure 1 mmol of β -ketoester was added to 10 mL of 0.01 molar solution of ytterbium triflate. To this mixture were added 3 equiv. of α,β -unsaturated ketone and the mixture was stirred for 3 to 5 days at RT in order to complete the reaction. The volatile components (excess enones) were evaporated under reduced pressure and the remaining aqueous solution was extracted three times with 10 mL of methylene chloride. The solvent of the combined organic fractions was evaporated under reduced pressure and the residue was stripped with toluene to give the pure Michael adducts in quantitative yield. (When the solvent was dried with sodium or magnesium sulfate the isolated yield dropped considerably presumably due to strong complexation). When non-volatile enones were used the Michael adducts could be isolated in nearly quantitative yield after column chromatography (SiO₂, ethyl acetate: hexane = 1 : 9). All compounds gave satisfactory spectroscopic and analytical data or data were in full agreement with these of known products. It should be noted that the aqueous catalyst solution could be reused without loss of catalytic activity.
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