Highly Efficient Ytterbium Triflate Catalyzed Michael Additions of α-Nitroesters in Water

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Abstract: Michael additions of α-nitroesters with enones and α,β-
unsaturated aldehydes result in quantitative conversions to the
corresponding 1,4-adducts by performing the reactions in water in the
presence of ytterbium triflate as water-tolerant Lewis acid.

In recent years there has been growing recognition that water is an
attractive medium for many organic reactions, in particular when one
considers the need to develop environmentally acceptable chemical
processes. Although it is by far the most common liquid in our
environment, water as a solvent was not frequently used until recently
for several reasons such as insolvability of the reactants or the reactivity
of reagents towards water. This is especially true for Lewis acids such as
AlCl₃, TiCl₄, or BF₃. Lanthanide triflates however have been described
as effective water-tolerant Lewis acids in several carbon-carbon
forming reactions such as Michael, aldol, and Diels-Alder reactions,
and in some cases the presence of water even improves their activity.
Nitroacetic acid derivatives are valuable intermediates for the
synthesis of many nitro and amino containing compounds. Michael
additions of 1 to enones opens a very attractive route towards functional
(α-alkylated) amino acids and substituted proline derivatives via
subsequent reductive cyclization of the nitro keto esters obtained
(Scheme 1). However, Michael reactions of α-nitro esters under basic
conditions often suffer from low yields.

To our knowledge, only one example of a Lewis acid catalyzed Michael
addition of α-nitroesters has appeared in the literature. Rather drastic
conditions were however required in this reaction catalyzed by copper(II) acetate in refluxing dioxane and reaction times of six days
were needed.

As part of our interest in catalytic carbon-carbon bond forming
reactions by conjugate addition reactions, we reported the catalytic
Michael addition of β-ketoesters towards enones and α,β-unsaturated
aldehydes in water, resulting in the corresponding Michael adducts in
nearly quantitative yield. These very promising results prompted us to
investigate the use of lanthanide triflates as reusable Lewis acid
catalysts in Michael reactions of α-nitroesters in water as the solvent.
We now report a highly efficient catalytic Michael addition of α-
nitroesters in water at room temperature in the presence of a catalytic
amount of ytterbium triflate (Yb(OTf)₃) as Lewis acid. When the 1,4-
addition of methyl nitroacetate (1a) to methyl vinyl ketone (5a, R³=H, MVK) was performed in water in the presence of 10 mol% of
Yb(OTf)₃, the Michael adduct 6 was isolated in a quantitative yield,
when two equivalents of MVK were used. With one equivalent of MVK
the mono-Michael adduct 7 was found exclusively (Table 1).

<table>
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<th>Entry</th>
<th>Michael donor</th>
<th>Michael adduct</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>1a</td>
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<td>99</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>7a</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>7b</td>
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</tr>
<tr>
<td>4</td>
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<td>7c</td>
<td>98</td>
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<tr>
<td>5</td>
<td>1d</td>
<td>7d</td>
<td>96</td>
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* Catalyst Yb(OTf)₃ solvent H₂O; Michael acceptor MVK

Also α-nitroesters bearing an alkylsubstituent at the α-position gave
the corresponding Michael adducts in quantitative yield in the reaction
with MVK in water as the solvent in the presence of 10 mol% of
Yb(OTf)₃. In the absence of Yb(OTf)₃ the reaction is much slower,
giving a low conversion to the desired Michael adduct even after
prolonged reaction times. Unfortunately methyl-2-
nitrophenylpropionate (1e) proved to be unreactive under the present
conditions, giving only traces of the desired Michael adduct and mainly
recovery of the starting material even after prolonged reaction times.

It should be emphasized that single products were obtained using this
simple procedure and in most cases no further purification was
necessary, since the Michael addition was not accompanied by unwanted O-alkylation or hydrolysis of the ester functionality. Furthermore, α,β-unsaturated enones bearing various substituents at the α'-position 5b-d were employed, again quantitative yields of the 1,4-adducts were found; typical examples are listed in Scheme 2. However, when cyclic or β-substituted α,β-unsaturated enones were used no reaction was observed even after prolonged reaction times and only starting materials were recovered. With the Michael acceptors bearing various electron withdrawing groups only acrolein did give the desired 1,4-adduct, whereas α,β-unsaturated esters or nitriles are not reactive under these conditions. This trend in reactivity in water was also observed for the Yb(OTf)₃ catalyzed Michael addition of α,β-ketoesters.¹⁰

As an example of a Michael acceptor bearing a substituent at the α-position methacrolein was reacted with 1b. Although the reaction afforded Michael adducts 7b and 7l as a mixture of diastereoisomers a reaction time of 170h was required to give nearly complete conversion in nearly quantitative yield. When non-volatile enones were used no 1,4-adduct was detected, whereas with cyclic or β-substituted enones bearing various electron withdrawing groups only acrolein did give the desired 1,4-adduct, whereas α,β-unsaturated esters or nitriles are not reactive under these conditions. This trend in reactivity in water was also observed for the Yb(OTf)₃ catalyzed Michael addition of α,β-ketoesters.¹⁰

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References and Notes
11. In a typical procedure 1.0 mmol of α-nitroester was added to 10 ml of 0.01 M solution of ytterbium triflate. To this mixture were added 3 equiv. of α,β-unsaturated ketone and the mixture was stirred for 3 d at RT until complete conversion. The volatile components (excess enones) were evaporated under reduced pressure and the remaining aqueous solution was extracted three times with 10 mL of CH₂Cl₂. The solvent of the combined organic fractions was evaporated under reduced pressure and the residual colorless oil stripped with toluene to give the pure Michael adduct as depicted in Scheme 4.

14. This side reaction was not observed for the other Michael acceptors used.

15. A mixture of 1.0 g (4.99 mmol) of ethyl-2-nitro-2-methyl-5-oxo-hexanoate (**7b**), 0.5 g Na$_2$SO$_4$ and 0.25 g 10% palladium on carbon in 25 mL anhydrous ethanol was shaken in a Parr apparatus for 72 h. After filtration over celite, the solvent was removed *in vacuo* and the residual oil was dissolved in 100 mL dry diethyl ether. HCl was bubbled through for 30 min. during which the hydroxyl pyrrolidine (mixture of *cis* and *trans* isomers) crystallized as the HCl-salt: (0.754 g white powder, 3.4 mmol, 69%).

8 *Cis* isomer: $^1$H-NMR(DMSO-$d_6$, 300 MHz, 100°C): $\delta = 1.20$ (t, $J=7.2$ Hz, 3H), 1.39 (d, $J=6.4$ Hz, 3H), 1.45 (s, 3H), 1.48-1.62 (m, 1H), 1.82-1.92 (m, 1H), 2.02-2.13 (m, 1H), 2.29-2.38 (m, 1H), 3.63-3.72 (m, 1H), 4.15 (dq, $J_1=0.2$ Hz, $J_2=7.2$Hz, 2H); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz, 100°C): $\delta = 13.23$ (q), 14.83 (q), 18.13 (q), 25.60 (t), 30.61 (t), singlet missing: under DMSO resonance, 61.00 (t), 62.58 (d), 132.2 (s).

9 *Trans* isomer: $^1$H-NMR(DMSO-$d_6$, 300 MHz, 100°C): $\delta = 1.20$ (t, $J=7.2$ Hz, 3H), 1.36 (d, $J= 6.6$Hz, 3H), 1.61 (s, 3 H), 1.54-1.63 (m, 1H), 1.85-2.39 (m, 3H), 3.82 (m, 1H), 4.24 (q, $J= 7.2$ Hz, 2H); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz, 100°C): $\delta = 16.65$ (q), 19.78 (q), 21.20 (q), 29.65 (t), 35.60 (t), singlet missing: under DMSO resonance, 54.38 (d), 71.73 (t), 170.34 (s); MS=188[M$^+$+1].