

A Novel Mannich-type Reaction in Aqueous Media. Lanthanide Triflate-catalysed Condensation of Aldehydes, Amines and Vinyl Ethers for the Synthesis of β -Amino Ketones

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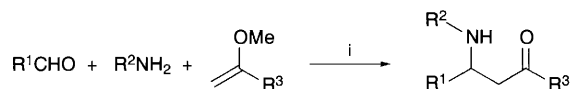
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A novel Mannich-type reaction between an aldehyde, an amine and a vinyl ether is catalysed by lanthanide triflates to afford a β -amino ketone in good yield in aqueous media.

The Mannich and related reactions provide one of the most fundamental and useful methods for the synthesis of β -amino ketones. Although the classical protocols include some severe side reactions, new modifications using preformed iminium salts and imines have been developed.¹ These materials are, however, often hygroscopic and are unstable at high temperatures. The direct synthesis of β -amino ketones from aldehydes is desirable from a synthetic point of view.

On the other hand, organic reactions in aqueous media are now of great interest.² We recently found that lanthanide triflates are stable Lewis acids in aqueous media that efficiently catalyse reactions of carbonyl and related compounds.³ In the course of our investigations to develop new synthetic reactions using these novel water-tolerant Lewis acid catalysts, lanthanide triflates were found to be effective for a novel Mannich-type reaction. Here we describe the lanthanide triflate-catalysed condensation of aldehydes, amines and vinyl ethers for the synthesis of β -amino ketones.

A general scheme for the new Mannich-type reaction is shown below (Scheme 1). A typical experimental procedure is as follows. In the presence of 10 mol% of ytterbium triflate [Yb(OTf)₃, a representative lanthanide triflate], an aldehyde, an amine and a vinyl ether were combined in a mixture of THF-

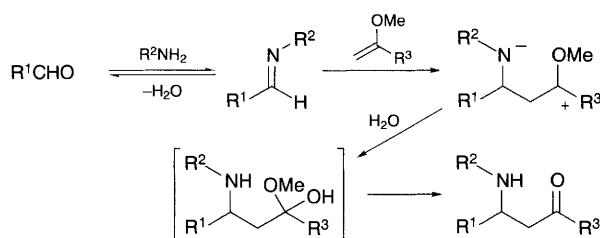


Scheme 1 Reagents and conditions: i, Yb(OTf)₃ (10 mol%), THF-H₂O (9:1)

Table 1 Synthesis of β -amino ketones in aqueous media

R ¹	R ²	R ³	Yield (%)
H	<i>p</i> -ClC ₆ H ₄	Me	92
H	<i>p</i> -Ans ^a	Me	76
H	<i>p</i> -Ans ^a	Ph	quant.
Ph	<i>p</i> -ClPh	Me	90
Ph	<i>p</i> -Ans ^a	Me	74
Ph(CH ₂) ₂	<i>p</i> -ClC ₆ H ₄	Me	55
ClCH ₂	<i>p</i> -ClC ₆ H ₄	Me	59
PhCH=CH	<i>p</i> -ClC ₆ H ₄	Me	73
PhCO	<i>p</i> -ClC ₆ H ₄	Me	93
PhCO	Ph	Me	90
PhCO	<i>p</i> -Ans ^a	Me	75
PhCO	<i>p</i> -Ans ^a	Ph	85
MeO ₂ C	<i>p</i> -Ans ^a	Me	67
MeO ₂ C	<i>p</i> -Ans ^a	Ph	58

^a *p*-Ans = *p*-Anisidine.



Scheme 2

H₂O (9:1) at room temperature. The mixture was stirred for 12–24 h at the same temperature, and saturated aqueous sodium hydrogen carbonate was added. After extracting three times with ethyl acetate, the organic layers were combined and dried. The crude product was purified by silica gel column chromatography to afford a β -amino ketone.

Selected examples of the present reaction are shown in Table 1. In all cases, β -amino ketones were obtained in good yields. Several characteristic features are noteworthy in this reaction. First, the procedure is very simple, consisting of simply mixing an aldehyde, an amine, a vinyl ether and a small amount of lanthanide triflate in aqueous solution. The catalyst could be recovered after the reaction was completed and could be reused (1st run, 93%; 2nd run, 83%; 3rd run, 87%, in the reaction of phenylglyoxal monohydrate, *p*-chloroaniline, and 2-methoxypropene). Commercially available formaldehyde and chloroacetaldehyde water solutions were used directly and the corresponding β -amino ketones were obtained in good yields. Phenylglyoxal monohydrate, methyl glyoxylate, an aliphatic aldehyde and an α,β -unsaturated aldehyde also worked well to give the corresponding β -amino esters in high yields. In some Mannich reactions with preformed iminium salts and imines, it is known that yields are often low because of the instability of the imines derived from these aldehydes, or troublesome treatments are known to be required for their use.^{4†}

A possible mechanism for the present reaction is shown in Scheme 2. It should be noted that dehydration accompanied by imine formation and successive addition of a vinyl ether proceed smoothly in aqueous solution.⁵ Use of lanthanide triflate, a water-tolerant Lewis acid, is key and essential in this reaction.

In summary, the first aqueous Mannich-type reaction catalysed by a lanthanide triflate has been developed.

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Footnote

† Other lanthanide triflates can also be used. In the reaction of phenylglyoxal monohydrate, *p*-chloroaniline, and 2-methoxypropene, yields of 90% [Sm(OTf)₃], 94% [Tm(OTf)₃] and 91% [Sc(OTf)₃] were obtained.

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