$Ln(OTf)_3$- or $Cu(OTf)_2$-Catalyzed Mannich-Type Reactions of Aldehydes, Amines, and Silyl Enolates in Micellar Systems. Facile Synthesis of β-Amino Ketones and Esters in Water

Shu Kobayashi,* Tsuyoshi Busujima, Satoshi Nagayama

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

Fax +81 (3) 5684-0634, E-Mail: skobayas@mol.f.u-tokyo.ac.jp

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Abstract: In the presence of a catalytic amount of $Ln(OTf)_3$ or $Cu(OTf)_2$, three-component Mannich-type reactions of aldehydes, amines, and silyl enolates proceeded smoothly in micellar systems to afford the corresponding β-amino ketones or esters in high yields. These reactions were successfully carried out in water without using any organic solvents.

Key words: mannich reaction, aqueous reaction, lanthanide triflate, micellar system, benign chemical synthesis

Much attention has been focused on organic processes in water without use of harmful organic solvents, which is an environmentally-friendly methodology.[1] Recently, we found that lanthanide triflates are stable Lewis acids in aqueous media that efficiently catalyze reactions of carbonyl and related compounds.[2] In addition, $Sc(OTf)_3$-catalyzed aldol reactions of silyl enolates with aldehydes in pure water were found to proceed smoothly with the aid of a small amount of a surfactant such as sodium dodecyl sulfate (SDS).[3] In this micellar system, ketene silyl acetals, which are known to be hydrolyzed easily in the presence of even a small amount of water, reacted with aldehydes to afford the corresponding aldol adducts in high yields. These results indicated that an excellent hydrophobic reaction field would be formed under these conditions, and gave us an idea that Mannich-type reactions of aldehydes, amines, and silyl enolates would also proceed smoothly in such a micellar system.

The Mannich and related reactions provide one of the most fundamental and useful methods for the synthesis of β-amino ketones and esters.[4] Although the classical protocols include some severe side reactions, new modifications using preformed iminium salts and imines have improved the process. Some of these materials are, however, unstable and difficult to isolate, and deaminations of the products that occur under the reaction conditions still remain as problems. The direct synthesis of β-amino ketones from aldehydes, amines, and silyl enolates under mild conditions is desirable from a synthetic point of view.[5] Our working hypothesis is that aldehydes could react with amines in the hydrophobic micellar system in the presence of a catalytic amount of lanthanide triflate to produce imines, which could react with hydrophobic silyl enolates.[6,7] Milder reaction conditions using lanthanide triflate as a Lewis acid and water as a solvent were expected.

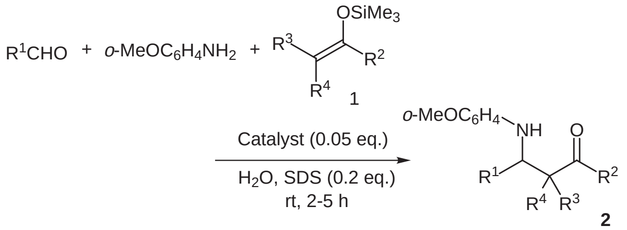

Table 1. Mannich-Type Reactions in Water

R^1	R^2	R^3	R^4	Catalyst	Yield/%
Ph	Ph	H	H	$Sc(OTf)_3$	87[a]
Ph	Ph	H	H	$Yb(OTf)_3$	80
Ph	Ph	H	H	$Cu(OTf)_2$	85
2-furyl	Ph	H	H	$Sc(OTf)_3$	85[b]
PhCO	Ph	H	H	$Sc(OTf)_3$	83
PhCH=CH	Ph	H	H	$Sc(OTf)_3$	74[b]
i-Bu	Ph	H	H	$Cu(OTf)_2$	76[b,c]
$Ph(CH_2)_2$	Ph	H	H	$Cu(OTf)_2$	80[b,c]
c-C_6H_{11}	Ph	H	H	$Sc(OTf)_3$	79[b,c]
Ph	MeO	Me	Me	$Sc(OTf)_3$	73
2-furyl	MeO	Me	Me	$Sc(OTf)_3$	80
PhCO	MeO	Me	Me	$Sc(OTf)_3$	67
PhCH=CH	MeO	Me	Me	$Sc(OTf)_3$	64
i-Bu	MeO	Me	Me	$Sc(OTf)_3$	88[c]
$Ph(CH_2)_2$	MeO	Me	Me	$Cu(OTf)_2$	82[c]
Ph	EtS	H	H	$Sc(OTf)_3$	68
Ph	EtS	Me	H	$Sc(OTf)_3$	85[d]
Ph	EtS	Me	H	$Cu(OTf)_2$	86[e]

[a] The same levels of yields were obtained when aniline, *p*-methoxyaniline, and *p*-chloroaniline were used instead of *o*-methoxyaniline. [b] Catalyst (0.1 eq.). [c] 0 °C. [d] *Syn*/*anti* = 3.0/1.[14] [e] *Syn*/*anti* = 2.7/1.[14]

First, a model reaction of benzaldehyde, *o*-methoxyaniline, and 1-phenyl-1-trimethylsiloxyethene was performed in the presence of 0.05 eq. of $Sc(OTf)_3$ in an aqueous solution of SDS (SDS, 0.2 eq., 35 mM). In a typical procedure, the amine and **1** were combined in the presence of $Sc(OTf)_3$ in 35 mM SDS, and then the aldehyde was added.[8] The reaction proceeded smoothly at room temperature to afford the corresponding β-amino ketone derivative **2** in 87% yield. It is noted that the dehydration (imine formation) and the coupling reaction between two water-unstable substrates, the imine and the silyl enol ether, occurred successfully in water.[9] Side reaction adducts such as deamination and aldol products were not obtained at all.[10] Other catalysts such as $Yb(OTf)_3$ and $Cu(OTf)_2$ were also found to be effective in this reaction.[11] We then tested other examples and the results are summarized in Table 1. Aromatic aldehydes as well as heterocyclic, α,β-unsaturated, aliphatic aldehydes, and a glyoxal worked well to afford the desired adducts in high yields. It is noteworthy that various types of aliphatic aldehydes reacted smoothly to give the corresponding β-amino ketone derivatives in high yields. For silyl enolates, not only ketone-derived silyl enol ethers but also thioester- and ester-derived ketene silyl acetals worked well.

The products were readily converted to free β-amino ketones and esters. Thus, treatment of the products with cerium ammonium nitrate (CAN) in acetonitrile-water (9:1) at rt induced smooth deprotection of the 2-methoxyphenylamino group to give free β-amino carbonyl compounds.[12,13]

In summary, three-component coupling reactions of aldehydes, amines, and silyl enolates were successfully performed in micellar systems using $Ln(OTf)_3$ or $Cu(OTf)_2$ as a catalyst. The reactions proceeded cleanly with a wide substrate range in water without using any organic solvents. This benign process will be applied to the synthesis of many β-amino carbonyl compounds including biologically interesting compounds, and such projects are now in progress in our laboratory.

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(8) A typical experimental procedure is as follows. To a 35 mM water solution of SDS (3 ml) and $Sc(OTf)_3$ (0.025 mmol) were added an amine (0.5 mmol), a silyl enolate (0.5 mmol), and an aldehyde (0.55-0.65 mmol) successively, and the mixture was stirred at rt. After 5 h, the mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried, filtered, and concentrated. The crude adduct was purified by column chromatography on silica gel to afford the pure desired β-amino carbonyl compound.

(9) Only a trace amount of the product was obtained without SDS under the same reaction conditions.

(10) Similar reactions performed in organic solvents sometimes induced certain amounts of deamination products.

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