

Novel One-pot Mannich-type Reaction in Water: Indium Trichloride-catalyzed Condensation of Aldehydes, Amines and Silyl Enol Ethers for the Synthesis of β -Amino Ketones and Esters

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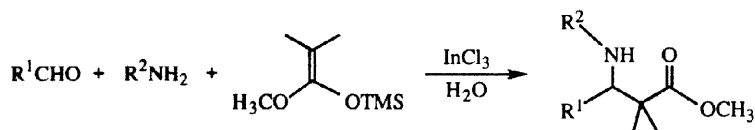
Received 6 October 1997; accepted 24 October 1997

Abstract: Novel one-pot Mannich-type reaction between aldehydes, amines and silyl enol ethers is catalyzed by indium trichloride in water to give β -amino ketones and esters in moderate to good yields.
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Organic reactions in water or aqueous media have always attracted great interest.¹ Recently, we have reported indium trichloride as an excellent catalyst in Mukaiyama aldol reactions,² Diels-Alder reactions,³ Michael reactions⁴ and the synthesis of α or β -trifluoromethylated alcohols⁵ neat and/or in water. Indium trichloride is stable in water, which can be recovered and reused on completion of these reactions. As it has unique properties compared to other Lewis acids, the application of this Lewis acid for other C-C bond formation reaction in water will be of great interest. In the course of our investigations, we have found that indium trichloride is also an efficient catalyst for the reaction of silyl enol ethers with imines in water.

As Aldol-Mannich type reaction is among the most fundamental and useful methods for the synthesis of β -amino ketones and esters, yields are however sometimes low due to severe side reactions such as deamination. Some new modifications have been developed in these two decades⁶ which include Lewis acid-catalyzed⁷ reactions of imines with silyl enol ethers to prepare β -amino esters and ketones. However, many imines are hygroscopic, unstable at high temperature, and difficult to purify by distillation or column chromatography. So it is desirable from a synthetic point of view that imines, generated from aldehydes and amines, immediately react with silyl enolates and provide β -amino ketones and esters preferably in a one-pot reaction. Unfortunately, most Lewis acids are not stable in this reaction as they decompose or deactivate in the presence of the water resulting from imine formation as well as from the direct attack by free amine present. In this article, we will describe an efficient one-pot method for the preparation β -amino esters and ketones from aldehydes using InCl_3 as catalyst in water (Scheme 1 and 2).

A general scheme for preparing β -amino esters in water is shown in Scheme 1. In the same vessel, a catalytic amount of indium trichloride (20 mol%), an aldehyde, an amine and the ester derived silyl enol ether (1-methoxy-2-methyl-1-trimethylsiloxypropene) were simply mixed in water in that order. The corresponding β -amino esters were formed in moderate to good yields (Table 1).

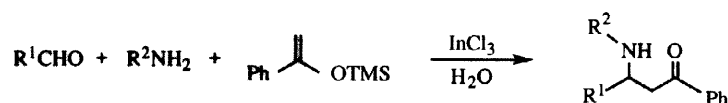


Scheme 1

Table 1. Synthesis of β -Amino Esters in Water: Using 1-Methoxy-2-methyl-1-trimethylsiloxypropene

Entry	Aldehyde	Amine	Yield % ^a
1	HCHO	PhNH ₂	30, 8 ^b
2	PhCHO	PhNH ₂	54
3	2-PyCHO	PhNH ₂	92
4	HCHO	4-ClPhNH ₂	21
5	PhCHO	4-ClPhNH ₂	23
6	2-PyCHO	4-ClPhNH ₂	90
7	HCHO	4-CH ₃ OPhNH ₂	35, 17 ^c
8	PhCHO	4-CH ₃ OPhNH ₂	30
9	2-PyCHO	4-CH ₃ OPhNH ₂	90

a. Isolated yield. b. Yield of PhN(CH₂C(CH₃)₂CO₂CH₃)₂. c. Yield of 4-CH₃OPhN(CH₂C(CH₃)₂CO₂CH₃)₂.

**Scheme 2**

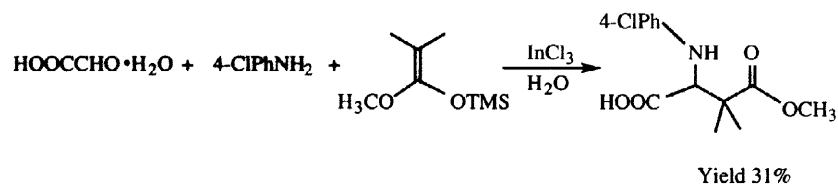
Application of this method to the ketone derived silyl enol ether (1-phenyl-1-trimethylsiloxyethylene) also afforded β -amino ketones (**Scheme 2**) in moderate to good yields (Table 2).

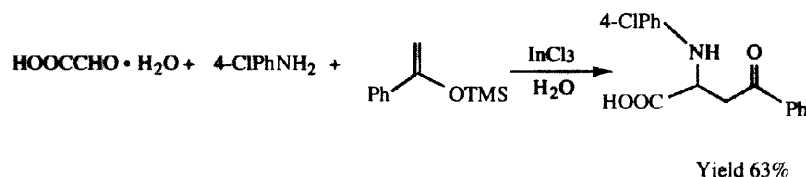
Table 2. Synthesis of β -Amino Ketones in Water: Using 1-Phenyl-1-trimethylsiloxyethylene

Entry	Aldehyde	Amine	Yield % ^a
1	HCHO	PhNH ₂	91 (88) ^b
2	PhCHO	PhNH ₂	75 (74) ^b
3	2-PyCHO	PhNH ₂	94
4	HCHO	4-ClPhNH ₂	85
5	PhCHO	4-ClPhNH ₂	60
6	2-PyCHO	4-ClPhNH ₂	91
7	HCHO	4-CH ₃ OPhNH ₂	86
8	PhCHO	4-CH ₃ OPhNH ₂	40
9	2-PyCHO	4-CH ₃ OPhNH ₂	90

a. Isolated yield. b. Yield (in parenthesis) obtained from using recovered InCl₃.

Furthermore, glyoxylic acid monohydrate can also be used directly to give the α -amino acids in moderate yields (**Scheme 3** and **4**). These results show a convenient method for the preparation of α -amino acids.

**Scheme 3**



Scheme 4

The experimental procedure is very simple. In the presence of indium trichloride (20 mol%), an aldehyde was treated with an amine in water and then with a silyl enol ether in the same vessel.⁸ It should be noted that in all cases dehydration accompanied by imine formation and successive addition of silyl enol ethers proceeded smoothly in water in the presence of indium trichloride. This water tolerant Lewis acid is essential and key to the success of this reaction as its absence only gave starting materials. This catalyst can be recovered and reused after completion of reactions without any decrease in yields. Under this reaction condition, commercially available formaldehyde solution and glyoxylic acid monohydrate can be used directly to give the corresponding β -amino ketones/esters and acids. In the classical Mannich reaction, deamination of Mannich bases to produce α,β -unsaturated derivatives resulted in undesirable side reactions. However, no deamination was observed under this reported condition. Furthermore, selective addition to the imines occur over the aldehydes as no reaction between aldehydes and the silyl enol ethers was observed.

In summary, this synthesis of β -amino ketones and esters from aldehydes have been achieved in water by using indium trichloride.⁹ The high efficiency using simple starting materials and a catalytic amount of a reusable catalyst in water is especially noteworthy. Further studies to apply this reaction to the synthesis of natural products as well as to develop new synthetic reactions using indium trichloride in conjunction with a water soluble ligand as a chiral catalyst are now in progress.

We acknowledge the financial support for this project from the National University of Singapore (Grant RP 940633, RP 950609, RP 970615 and RP 970616).

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8. A typical reaction procedure is as follows: The solution of 38% formaldehyde solution (0.5 mmol, 37 μ L), aniline (0.5 mmol, 46 μ L) in the presence of indium trichloride (22.1 mg, 0.1 mmol, 20 mol%) in water (5 mL) was stirred for half an hour and then 1-phenyl-1-trimethylsiloxyethylene (192.3 mg, 1 mmol) was added. The resulting mixture was stirred at room temperature for 24 h. The product was extracted with ethyl acetate three times and the organic layers were combined and dried with anhydrous magnesium sulphate. The solvent was evaporated and the crude product was purified by silica gel column chromatography to afford the β -amino ketone in 91% yield (102.5 mg).
9. These results are limited to non-enolizable imines. We have also investigated the aliphatic enolizable imines derived from alkyl aldehydes (such as valeraldehyde) and found the yields were poor.