

Ytterbium(III) Triflate-Catalyzed One-Pot Mannich-Type Reaction in Ionic Liquid

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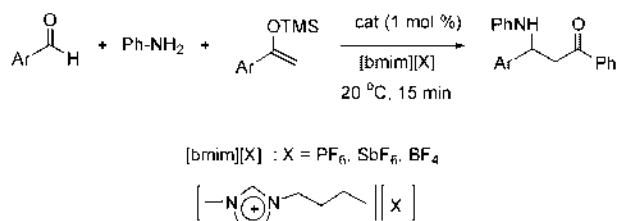
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The Lewis acid-catalyzed reactions of imines with enolate components are useful methods for the preparation of β -amino ketones or β -amino esters, leading to β -lactam derivatives.¹ As for the reactions using silyl enolates, use of a stoichiometric amount of TiCl_4 as a promoter was first reported in 1977.² Since then, some methodologies that report the catalytic use of Lewis acid promoters such as TMSOTf ,^{3a} phosphonium salts,^{3b} FeI_2 ,^{3c} trityl hexafluoroantimonate,^{3c} and $\text{B}(\text{C}_6\text{F}_5)_3$ ^{3d} were published. A great advance in catalytic Lewis acid Mannich-type reaction was described by Kobayashi that reported the discovery of a highly efficient one-pot three component reaction of aldehydes, amines and enolates with the use of rare earth metal triflates such as ytterbium triflate, $\text{Yb}(\text{OTf})_3$, and scandium triflate, $\text{Sc}(\text{OTf})_3$.⁴ More recently, Loh found that indium trichloride, InCl_3 , also can be an efficient catalyst for the three component synthesis of β -amino esters.⁵ The preferential coordination ability of the water-tolerant Lewis acids to aldimine over aldehyde^{5b,6} made the reactions possible in a mixture of $\text{THF-H}_2\text{O}$ (9:1) with $\text{Yb}(\text{OTf})_3$ ^{4b} or in pure H_2O with InCl_3 ,⁵ in which, however, rather longer reaction time (12-24 h in the presence of 10-20 mol% of catalyst) is required to completion. Recently, we found that the lanthanide triflates are stable and effectively catalyzed the three component one-pot Mannich-Felds reaction of aldehydes, amines and phosphorus nucleophiles affording α -amino phosphonates in room temperature ionic liquids,⁷ in particular, consisting of 3-butyl-1-methylimidazolium (bmim) cations.⁸ Moreover, the reaction rate of the reaction was largely accelerated in ionic liquids compared to in organic or water solvents.⁹ These results prompt us to examine the one-pot Mannich-type reactions affording β -amino ketones and esters in environmentally benign ionic liquids, $[\text{bmim}][\text{X}]$, using the Lewis acids, $\text{La}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$ and InCl_3 as catalysts (Scheme 1).

As a model reaction, the three component reaction of



Scheme 1

benzaldehyde, aniline and acetophenone trimethylsilylenolates has been carried out at 20 °C using 1 mol % of $\text{Yb}(\text{OTf})_3$ in $[\text{bmim}][\text{PF}_6]$ (5 equivalent, 1 mL).¹ After 15 min, product can be isolated in 85% yield (entry 1). However, the insolubility of the product in ionic liquid hindered the stirring of the reaction mixture, which could be overcome by employing benzene (2 mL) as a co-solvent, and afforded product in 91% yield within 15 min (entry 2). Even in the presence of 0.1 mol % of $\text{Yb}(\text{OTf})_3$, the reaction proceeded smoothly with a 80% yield within 15 min (entry 3). When the same reaction was conducted in benzene solvent only, the product was formed in 50% yield in 24 h (entry 4). These results indicate that the $[\text{bmim}][\text{PF}_6]$ played a crucial role for the increased catalytic activity. Of special interest was the fact that the ionic liquid itself has catalytic property. Thus, the reaction without $\text{Yb}(\text{OTf})_3$ for 26 h afforded 55% yield of adduct (entry 5). The yield was increased slightly as increase the amount of ionic liquid (60% yield, entry 6). Since fluoride anion can be an efficient activator for Mukaiyama aldol-type reactions,¹⁰ it could not be excluded the possibility that the fluoride anion generated from PF_6^- acts as a catalyst for this three component Mannich-type reaction. However, other ionic liquids such as $[\text{bmim}][\text{SbF}_6]$ and $[\text{bmim}][\text{BF}_4]$ did not show such catalytic activity. The reactions using other catalysts such as $\text{Sc}(\text{OTf})_3$ (76%, entry 7) and InCl_3 (70%, entry 8) or other ionic liquids, $[\text{bmim}]$ -

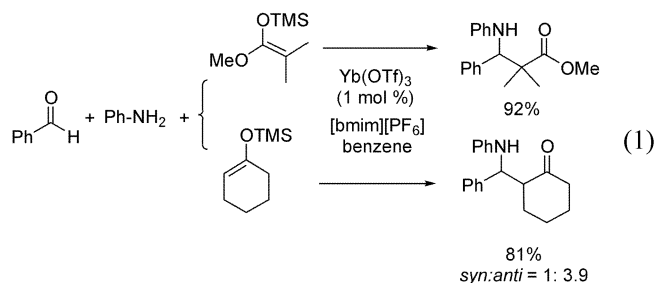
Table 1. Three components One-Pot Mannich-type reactions of aldehydes, aniline and acetophenone trimethylsilylenolates in $[\text{bmim}][\text{X}]$

Entry	Ar	Catalyst	X	Yield ^a
1 ^b	Ph	$\text{Yb}(\text{OTf})_3$	$[\text{PF}_6]$	85
2	Ph	$\text{Yb}(\text{OTf})_3$	$[\text{PF}_6]$	91
3 ^c	Ph	$\text{Yb}(\text{OTf})_3$	$[\text{PF}_6]$	80
4 ^d	Ph	$\text{Yb}(\text{OTf})_3$	—	50
5 ^e	Ph	—	$[\text{PF}_6]$	55
6 ^f	Ph	—	$[\text{PF}_6]$	60
7	Ph	$\text{Sc}(\text{OTf})_3$	$[\text{PF}_6]$	76
8	Ph	InCl_3	$[\text{PF}_6]$	70
9	Ph	$\text{Yb}(\text{OTf})_3$	$[\text{SbF}_6]$	72
10	Ph	$\text{Yb}(\text{OTf})_3$	$[\text{BF}_4]$	47
11	3-Thiophenyl	$\text{Yb}(\text{OTf})_3$	$[\text{PF}_6]$	97
12 ^g	2-Pyridyl	$\text{Yb}(\text{OTf})_3$	$[\text{PF}_6]$	70
13 ^h	1-Naphthyl	$\text{Yb}(\text{OTf})_3$	$[\text{PF}_6]$	78

^aIsolated yield. ^bReaction without benzene. ^cReaction with 0.1 mol% of $\text{Yb}(\text{OTf})_3$. ^dReaction in benzene only. ^eReaction for 24 h. ^fReaction in 10 equiv. of $[\text{bmim}][\text{PF}_6]$. ^gReaction for 30 min.

[SbF₆] (72%, entry 9) and [bmim][BF₄] (47%, entry 10) afforded the product with relatively lower yields. Reaction of silyl enol ether of acetophenone and aniline with other aldehydes such as 3-thiophenecarboxaldehyde (97%, entry 11), 2-pyridinecarboxaldehyde (70%, entry 12), 1-naphthaldehyde (78%, entry 13) using 1 mol% of Yb(OTf)₃ in [bmim][PF₆] afforded the corresponding β-amino ketones in good yields.

Having ascertained the efficiency of Yb(OTf)₃-catalyzed three component Mannich-type reaction in an ionic liquid, [bmim][PF₆], involving a silyl enol ether of acetophenone, this methodology was extended to another acyclic silyl enol ether, 1-methoxy-2-methyl-1-trimethylsilyloxypropene, to give methyl 2,2-dimethyl-3-(*N*-phenylamino)-3-phenylpropionate in 92% yield. Also, a cyclic silyl enol ether, trimethylsilyloxycyclohexene was reacted with benzaldehyde and aniline to give the desired product in good yield (81%) with *anti*-selectivity (*syn:anti* = 1 : 3.9) (Equation 1).



In summary, we have demonstrated that ionic liquids act as powerful reaction media for Yb(OTf)₃-catalyzed three component one-pot Mannich-type reaction of aldehydes, an amine and silyl enol ethers. It has been also found that [bmim][PF₆] itself act as a catalyst. Further studies on the effect of rate acceleration and catalytic property of the ionic liquids are underway.

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Notes and References

¹A typical procedure for the three component reactions in ionic liquid: Aniline (0.13 g, 1.48 mmol), benzaldehyde (0.1 g, 0.98 mmol) and acetophenone trimethylsilylenolate (0.28 g, 1.48 mmol) were successively added to a solution of Yb(OTf)₃ (6.1 mg, 9.8 × 10⁻³ mmol) in [bmim][PF₆] (1 mL)/benzene (2 mL) at 20 °C. After stirring the reaction mixture for 15 min, the insoluble solid was filtered. The filter cake was dissolved in CH₂Cl₂, and the organic layer was washed with water. Evaporation of the CH₂Cl₂ afforded pale brownish solid, which was treated with MeOH to give 3'-phenyl-3'-(*N*-phenylamino)-propiofenone (0.27 g, 91%) as a white solid.

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