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$Y(NO_3)_3 \cdot 6H_2O$ catalyzed aza-Michael addition of aromatic/hetero-aromatic amines under solvent-free conditions

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Abstract

The aza-Michael addition of weakly nucleophilic amines with α, β-unsaturated compounds like esters, nitriles and amides has been carried out efficiently using $Y(NO_3)_3 \cdot 6H_2O$ as a novel catalyst under solvent-free conditions. The catalyst exhibited remarkable activity and the methodology was applicable to a wide variety of aryl/hetero-aryl amines having different steric and electronic properties giving high yields of desired adducts at ambient conditions.

Keywords: Aza-Michael; Yttrium(III) nitrate hexahydrate; Solvent-free; Amines; *N*-heterocycles

1. Introduction

β-Amino esters and their derivatives are useful building blocks for the molecules with applications in pharmaceuticals and fine chemicals. They are versatile intermediates for the synthesis of biologically important natural products and antibiotics [1]. The Mannich-type reactions are classical methods for the synthesis of β-amino compounds. However, the reaction is associated with disadvantages like drastic reaction conditions and longer reaction times. Alternatively, the conjugate addition of amines to α, β-unsaturated compounds (aza-Michael reaction) is an attractive route for their synthesis. The reaction is atom economic and carried out in presence of an acid or a base [2]. The Michael addition of aliphatic amines to α, β-unsaturated compounds is well known [3–9] and the reaction proceeds even without a catalyst [10,11]. In contrast, aromatic amines being weakly nucleophilic do not undergo such additions easily and developing an efficient protocol for them still remains a challenging task. Very few reports involving catalysts or reagents like CAN [12], silica gel [13], samarium diiodide [14], $RuCl_3$/PEG [15], $InCl_3$ [16] are known to affect these transformations. Recently, the use of microwave technique using stoichiometric amount of acetic acid at high temperature has been reported [17]. However, requirement of elevated temperatures, lower substrate compatibility, high cost of catalyst, longer reaction time, use of hazardous solvents limits their applications. Thus, there was a need to develop an efficient catalytic protocol that could overcome above mentioned disadvantages and facilitate the addition of both aromatic/hetero-aromatic amines to α, β-unsaturated compounds.

In our previous study [18], we had introduced $Y(NO_3)_3 \cdot 6H_2O$, as a novel and reusable catalyst for one pot synthesis of 3, 4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. The catalyst had shown remarkable activity and reusability. The coordinating ability of $Y(NO_3)_3 \cdot 6H_2O$ along with its commercial availability prompted us to further investigate its activity for aza-Michael reaction. In continuation of our work on addition of amines to C–C double bond and C–N coupling reactions [19], we herein report highly efficient catalytic protocol for 1, 4-addition of amines to α, β-unsaturated compounds providing the

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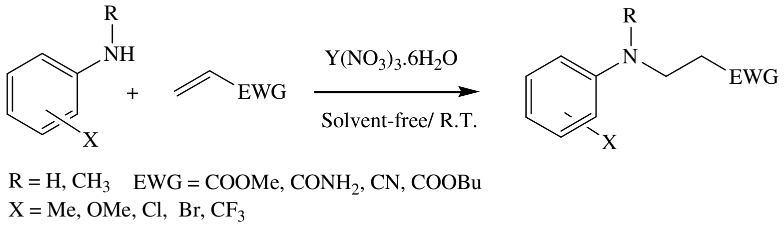

Scheme 1. Aza-Michael addition of aromatic amines to α, β-unsaturated compounds under solvent-free conditions.

corresponding *N*-aryl and *N*-hetero-aryl functionalized β-amino compounds in excellent yields under solvent-free conditions (Scheme 1).

2. Experimental

2.1. General

All chemicals and catalysts were procured from firms of repute and used without any further purification. $Y(NO_3)_3 \cdot 6H_2O$ (99.9%) was purchased from Lancaster and used as received. The conversions were based on GC analysis (Chemito 1000). All products were characterized by GC-MS analysis (Shimadzu QP2010). ^1H and ^{13}C NMR spectra were recorded on Varian-300 NMR spectrometer using TMS as an internal standard.

2.2. Typical procedure for aza-Michael addition of aromatic amines to α,β-unsaturated compounds

A mixture of amine (5 mmol), α, β-unsaturated compound (2.5 mmol) and $Y(NO_3)_3 \cdot 6\,H_2O$ (0.25 mmol) was stirred at room temperature. The progress of the reaction was monitored using a gas chromatograph (Chemito 1000). After completion, the product was isolated by silica gel chromatography using pet ether/ethyl acetate system.

2.3. Typical procedure for aza-Michael addition of hetero-aromatic amines to α,β-unsaturated compounds

A mixture of hetero-aromatic amine (2.5 mmol), α, β-unsaturated compound (2.5 mmol) and $Y(NO_3)_3 \cdot 6H_2O$ (0.25 mmol) was stirred at room temperature. The progress of the reaction was monitored using a gas chromatograph (Chemito 1000). After completion, the product was isolated by silica gel chromatography using chloroform/methanol system.

2.4. Spectral data of selected products

Table 2, entry 1: ^1H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 2.60$ (t, $J = 6.42$ Hz, 2H), 3.43 (t, $J = 6.42$ Hz, 2H), 3.68 (s, 3H), 6.62 (d, Ar2H) 6.73 (t, Ar1H), 7.16 (t, Ar2H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 33.6$,

Table 1
Influence of reaction parameters on aza-Michael addition of aniline with methyl acrylate[a]

No.	Solvent	Catalyst	Catalyst loading (mol %)	Yield (%)
Influence of solvent				
1	Ethanol	$Y(NO_3)_3 \cdot 6H_2O$	10	10
2	Acetonitrile	$Y(NO_3)_3 \cdot 6H_2O$	10	12
3	Dichloromethane	$Y(NO_3)_3 \cdot 6H_2O$	10	3
4	Toluene	$Y(NO_3)_3 \cdot 6H_2O$	10	18
5	None	$Y(NO_3)_3 \cdot 6H_2O$	10	87
Influence of catalyst				
6	None	$Y(NO_3)_3 \cdot 6H_2O$	10	87
7	None	$Cu(NO_3)_2 \cdot 3H_2O$	10	30
8	None	$Zn(NO_3)_2 \cdot 6H_2O$	10	55
9	None	$Bi(NO_3)_3 \cdot 5H_2O$	10	45
10	None	$Fe(NO_3)_3 \cdot 9H_2O$	10	62
11	None	$AlCl_3$	10	15
12	None	$FeCl_3$	10	17
Influence of catalyst loading				
13	None	$Y(NO_3)_3 \cdot 6H_2O$	12.5	88
14	None	$Y(NO_3)_3 \cdot 6H_2O$	10	87
15	None	$Y(NO_3)_3 \cdot 6H_2O$	7.5	71
16	None	$Y(NO_3)_3 \cdot 6H_2O$	5	66
17	None	$Y(NO_3)_3 \cdot 6H_2O$	2.5	60
18	None	None	–	–

[a] Reaction conditions: aniline = 5 mmol; methyl acrylate = 2.5 mmol; solvent = 3 ml, time = 3 h. GC yields.