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Indium Triflate Catalyzed Michael Addition of Amines to a,β-Unsaturated Esters and Nitriles: Synthesis of β-Amino Esters and Nitriles

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Amine undergoes Michael addition with α,β-unsaturated esters and nitriles to form β-amino esters and nitriles in excellent yields under mild conditions.

Key Words: Indium triflate, Michael addition, β-Amino acids, Esters, Nitriles.

INTRODUCTION

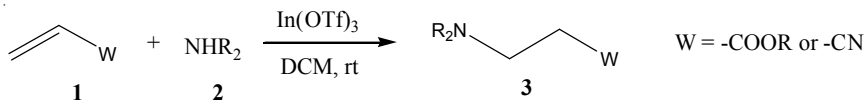
During the last few years, the preparation of enantiopure β-amino acids has emerged as an important and challenging synthetic endeavor. The increasing attention given to the chemistry of β-amino acids is partly due to the fact that they are components of a variety of natural products such as taxol[1], the dolastamines[2] and many others[3]. Furthermore a numbers of β-amino acids show interesting pharmacological properties in free form[4] or as their cyclized (β-lactam) derivatives[5]. A number of research groups have also embarked on the synthesis of oligomers from β-amino acids, which give rise to stabilized helical structures and can exhibit a resistance to enzymatic hydrolysis[6,7]. In the recent years indium was found as an efficient catalyst in various synthetic transformations. Indium mediated reactions have emerged as a useful tool in organic synthesis[8,9]. In particular, it was found that the low increased by the formation of complexes organolithium compounds[10-12]. The tetraorgano indates thus prepared are sufficiently reactive to take part in reactions at ambient temperature[13]. Allylic indates react with imides and nitriles regioselectively at the γ-carbon to give homoallyl-amines[14]. Organoindium compounds derived from dibromo substituted active methylene compounds such as dibromomalanonitrile and indium metal react with alkenes and carbonyl compounds to give cyclopropenes and oxiranes, depending on the nature of the reagents and substrates[15,16]. Here we found that indium triflate efficiently catalyzes the Michael addition of amines to α,β-unsaturated esters and nitriles under mild conditions and described the synthesis of β-amino esters and nitriles using indium-triflate.

EXPERIMENTAL

General procedure (3): A stirred solution of diethyl amine (212 mg, 2 mmol) and methyl acrylate (140 mg, 2 mmol) in dichloro methane (DCM) was added indium triflate (630 mg, 2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. After work-up, the solution was concentrated and the crude mixture was separated by column chromatography over silica gel to give methyl 3-(diethylamino) propanoate. The organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was separated by column chromatography over silica gel (ethyl acetate-hexane, 4-6) (95 % Yield).

RESULTS AND DISCUSSION

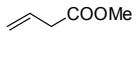
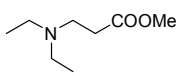
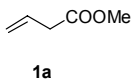
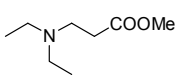
Intially, the reaction was carried out by the reaction of methyl acrylate and diethyl amine. The TLC observation showed the completion of the reaction after 1 h. After work-up, the product was purified over silica gel and confirmed as **3a** by spectroscopic data and compared with literature data (95 % yield) (**Scheme-I**).

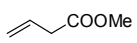
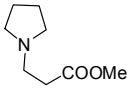
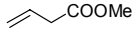
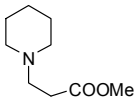
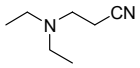
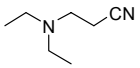
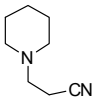


Scheme-I

Similarly, various amines and α,β-unsaturated esters and nitriles were reacted in the presence of indium triflate under similar condition to give the corresponding β-amino esters and nitriles in good yield. The reaction worked well both with aliphatic esters and nitriles. In all the cases, the reaction proceeded efficiently under moderate conditions giving excellent yields (Table-1).

TABLE-1
INDIUM TRIFLATE CATALYZED MICHAEL ADDITION OF AMINE TO α,β-UNSATURATED ESTERS AND NITRILES

Entry	Amine	α,β-unsaturated ester or nitrile	Products[a]	Yield (%)[b]
1				95
	1a	**2a**	**3a**	
2				90
	1a	**2b**	**3b**	

Entry	Amine	α,β-unsaturated ester or nitrile	Products[a]	Yield (%)[b]
3	 **1a**	 **2c**	 **3c**	93
4	 **1a**	 **2d**	 **3d**	89
5	 **1b**	 **2e**	 **3e**	91
6	 **1b**	 **2f**	 **3f**	92
7	 **1b**	 **2g**	 **3g**	93
8	 **1b**	 **2h**	 **3h**	90

a: All the products were characterized by ^{1}H NMR and mass spectroscopy.
b: Isolated yields after column chromatography.

Conclusion

In summary, a simple and efficient protocol for the preparation of β-amino esters and nitriles through the Michael addition of amines and α,β-unsaturated esters and nitriles using indium triflate is described. The attractive features of this process are the mild condition and cleaner reactions with good yields, which makes it a useful process for the synthesis of β-amino esters and nitriles.

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