Michael addition of aromatic and aliphatic amines to unsaturated olefines in the presence of TMSCl under solvent free conditions

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Abstract

An operationally simple and highly fast protocol for TMSCl (10 mol%) catalyzed conjugate addition of aromatic and aliphatic amines derivatives to unsaturated carbonyl compounds in good to excellent yields has been developed.

Keywords: amines; Micheal; unsaturated carbonyl compounds; TMSCl

Introduction

The aza-Michael reaction is an important reaction in organic chemistry, especially for the synthesis of C-N heterocycles [1] containing the β-aminocarbonyl functionality, which not only constitutes a component of biologically active natural products but also serves as an essential intermediate in the synthesis of β-amino ketones, β-amino acids, and β-lactam antibiotics.[2] Such aza-Michael reactions have generally been promoted by harsh bases or strong acids, which give rise to environmentally hazardous residues and undesirable by-products.[3] With the goal of avoiding the typical disadvantages resulting from the presence of such catalysts, a large number of alternative procedures have been developed in the past few years.[4]

In contrast, the range of amine nucleophiles and Michael acceptors well suited for both catalytic and stoichiometric methodologies is generally restricted to simple aliphatic amines and enones, and there has been few straightforward reports involving catalysts or reagents were known to affect these transformations. [5] Thus, development of 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 is great challenges.

As a part of our research aimed at developing green chemistry by using water as the reaction medium or by performing organic transformations under solvent-free conditions, herein, we describe a simple, highly efficient and eco-friendly method for the synthesis of β-amino carbonyl compounds from aromatic and aliphatic amines and α,β-unsaturated Michael acceptors under solvent free conditions.

In our initial studies, to find the standard experimental procedure, *p*-methoxyaniline was treated with methyl acrylate with different ratios of TMSCl in different organic solvents. In the absence of TMSCl no reaction occurred after prolonged reaction time. The reaction was best carried out in the presence of 10 mole% of TMSCl at 60^{o}C under solvent free conditions. In organic solvent, such as CH_2Cl_2, CH_3CN the Michael addition reaction proceeded smoothly to give product in low yields with long reaction times. The best reaction condition was found when using 1 equiv of amine and 1 equiv of methyl acrylate under SFC conditions for 120 min in the presence of TMSCl (10 mol%) at 60 ^{o}C. The crude product was isolated after simple workup, affording Michael type products in 90% yield (scheme 1). To test the feasibility of a large-scale reaction, 1 (20 mmol) was treated with 2 (20 mmol) and TMSCl (2 mmol) at the same reaction conditions and the product was isolated in 80% yield after 2 h.

Encouraged by the remarkable results obtained with 4-methoxyaniline and methyl acrylate, a variety of substituted amine and electron deficient compounds were tested using this new Michael addition method. The results clearly demonstrate that TMSCl is an excellent catalyst for the Michael addition reaction at mild reaction conditions (Table 1). In all cases, reactions proceeded smoothly and gave the corresponding products in good to excellent yield. Both aliphatic and aromatic amines react with a variety of conjugated alkenes by this procedure to produce the corresponding adducts in high yields. As evident from the results, anilines bearing either electron-donating or electron-withdrawing groups

give the Michael addition products in good yields. Similarly, the corresponding products from the reaction of aliphatic amines with α,β-unsaturated alkenes were obtained with excellent yields. In general the reaction rates are faster with aliphatic amines compared to those of aromatic amines and very poor amines such as 4-nitroaniline did not react due to the decrease in nucleophilicity of the nitrogen atom of 4-nitroaniline. Primary amines produced only monoaddition products and no bis-addition product was isolated. Similarly, various α,β-unsaturated compounds such as methyl acrylate, acrylonitrile, acrylamide, chalcone, benzylidenacetone and cinnamonitrile underwent 1,4-addition with a variety of amines to furnish the corresponding addition products. Furthermore, reactive Michael acceptor such as methyl vinyl ketone to give Michael adducts under catalyst free conditions at room temperature with short reaction time. In all cases the reactions proceed at this temperature with high selectivity, and no 1,2-adduct were obsereved under these reaction conditions. In the case of sterically hindered and less reactive enone, such as chalcone, the reaction proceeds smoothly with good yield. (Table 1). However, α,β-unsaturated esters and aldehydes are not suitable substrates for Michael addition reaction of amines under these reacton conditions.

Although no detailed mechanistic studies have been carried out, the role of TMSCl in catalyzing the Michael addition of amine with enones maybe realized through the acivation of unsaturated carbonyl groups and rendering the enones more susceptible to nucleophilic attack by amine, following by hydrogen transfer to form the products.

In conclusion, we have developed an operationally simple and very mild process for Michael addition of amine derivatives in the presence of TMSCl catalyst. This reaction can be carried out in very simple manner, by just mixing of substrate with very small quantitative of catalyst. The high reactivity of catalyst and simplicity of workup procedure

with high purity and short reaction time provides a straightforward and practical process for Michael reaction in large scales.

Experimental

General Procedure for Michael reaction of amines and enones.

To the mixture of amines (1 mmol), an enones (1 mmol), TMSCl (10 mol%) was added at 60^{o}C and stirred for 2-4 h until the disappearance of the starting amine as indicated by TLC or GC. When the reaction was complete, water were added and organic phase were separated. The crude product was analyzed by NMR and purified by recrystallization or column chromatography (EtOAc–petroleum ether) to afford the pure products.

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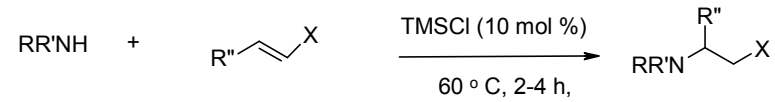
Table 1. Michael addition of amine to enones in the presence of TMSCl



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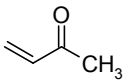
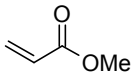
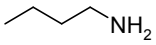
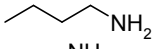
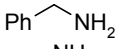
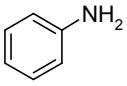
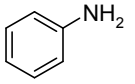
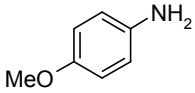
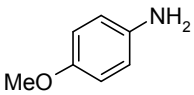
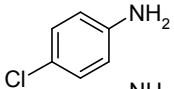
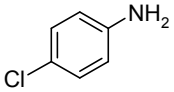
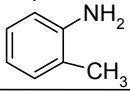
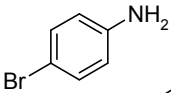
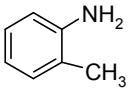
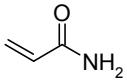
2			92	20			92
3			95	21			90
4			80	22			80
5			82	23			90
6			80	24			94
7			90	25			88
8			70	26			82
9			65	27			80
10			84	28			88
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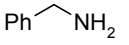
12			92	30			70
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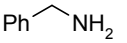
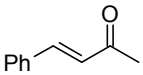
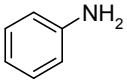
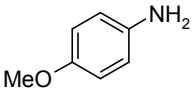
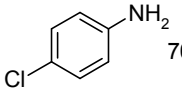
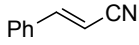
14			82	32			92
15			80	33			92
16			88	34			84
17			70	35			88
18			64	36			80

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