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$LiClO_4$ Accelerated Michael addition of amines to α,β-unsaturated olefins under solvent-free conditions

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Abstract—Several primary and secondary amines were added to α,β-unsaturated esters, nitriles, amides, and ketones to give the corresponding saturated amines mediated by solid lithium perchlorate under solvent-free and environmentally friendly conditions at room temperature.

1. Introduction

The synthesis of β-amino esters has gained considerable attention[1] due to their biologically important properties, their occurrence in natural products and their use as precursors for the preparation of β-lactams.[1] The β-amino acids, in free form, show interesting pharmacological properties. For instance, hypoglycemic and antiketogenic activities were observed in rats after oral intake of emeriamine. Functionalized β-amino acids are the key component of a variety of bioactive molecules such as taxol, which is one of the most active antitumor agents. During the past few years the synthesis of β-amino acid derivatives with different substitution patterns at the carbon chain has become a field of increasing interest in organic synthetic.[2] Among the different synthetic methodologies the literature for the preparation of β-amino esters, one of the simplest and most widely used methods is the conjugate addition of amines to α,β-unsaturated ester derivatives. Although Michael addition of amines to α,β-unsaturated acids failed, their addition to α,β-unsaturated nitriles, esters and ketones were known. These methods usually require basic conditions, or acid catalysis.[3] Also, a number of alternative procedures have been developed in the past few years and in particular, various Lewis acid-induced reactions have been reported.[4] Unfortunately, many of these procedures often require a large excess of reagents, long reaction time and drastic reaction conditions in acetonitrile or 1,2-dichloroethane which are toxic. In some cases, a stoichiometric amount of Lewis acid such as $AlCl_3$, $TiCl_4$ or $SnCl_4$ are required.[4]

Recently, $LiClO_4$ has emerged as a powerful promoter in many chemical processes and in different organic media.[5] In this context, it is worthy to note that, due to the remarkable tolerance of $LiClO_4$ toward coordinating functional groups, even strongly coordinating amines can be used in the presence of $LiClO_4$.[6] We have taken advantage of this compatibility in developing a practical, simple and environmentally benign methodology for the conjugate addition of amines to α,β-unsaturated esters, nitriles, amides and ketones under neutral and solvent-free conditions. So far there are not any reports in the literature on the Michael addition to α,β-unsaturated olefins mediated by $LiClO_4$ under solvent-free conditions. Herein we report the $LiClO_4$ accelerated Michael addition of amines to α,β-unsaturated compounds under solvent-free conditions and at room temperature.

The Michael reaction of pyrrolidine with methylacrylate in the presence of solid $LiClO_4$ gave the Michael adduct in high yield and in a short time. The results and conditions are summarized in Table 1. The data in Table 1 clearly show that the reaction of different aliphatic amines and methylacrylate give the corresponding β-amino ester in high yield at room temperature without using any solvent. Primary amines, such as butylamine and benzylamine reacted with α,β-unsaturated esters to give only the mono alkylated adduct. No side product was observed by using excess of the reactants. When aromatic amines, such as aniline, were added to α,β-unsaturated ester (entry 6, Table 1), the Michael adduct was formed in low yield. The difference in the reactivity of aromatic amines shows the chemoselectivity of Michael addition of aliphatic amines in this method. Thus, when a mixture of aniline and pyrrolidine were exposed to excess methylacrylate in the presence of solid $LiClO_4$, the pyrrolidine adduct was obtained as the sole product (Scheme 1).

Keywords: Michael addition; Amine; α,β-Unsaturated olefins; Lithium perchlorate.
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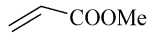
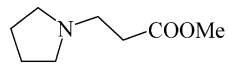
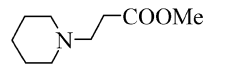
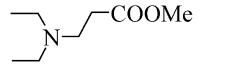
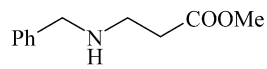
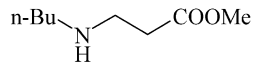
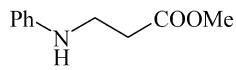
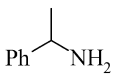
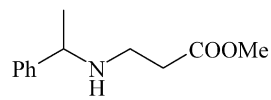
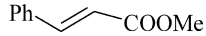
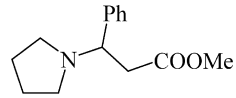
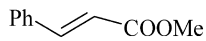
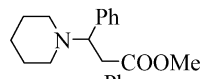
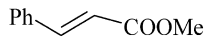
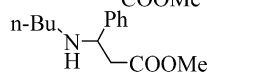
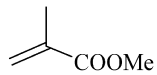
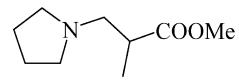
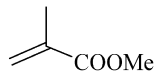
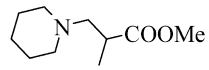
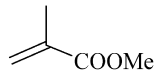
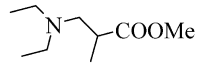
Table 1. Micheal addition of amines to α,β-unsaturated esters under solvent-free condition

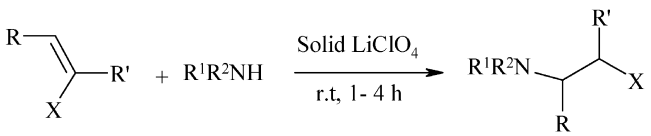
Entry	Amines	Ester	Product	Yield (%)[a] (time, h)[b]
1				86 (1)[4f]
2				84 (1)[4f]
3				88 (1)[4f]
4				89 (2)[1b]
5				90 (2)[1b]
6				30 (4)[1b]
7				88 (2)[1a]
8				80 (2)[4f]
9				76 (2)[4f]
10				60 (2)[1a]
11				90 (2)[1b]
12				86 (1.5)[1b]
13				80 (2)[1b]
14				78 (2)[1b]
15				82 (2)[1b]

[a] Isolated yields.
[b] References.

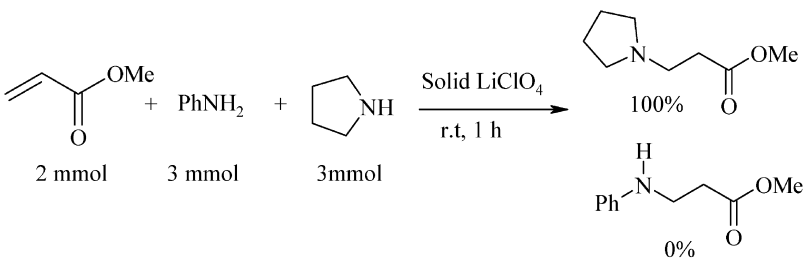
The Michael addition reaction of amines to α,β-unsaturated esters in the presence of solid $LiClO_4$ is temperature dependent. When the reaction was carried out at room temperature, only Michael adducts were formed. By elevating the temperature to 60 °C, the corresponding amides were obtained (Scheme 2).

This method also works well for α,β-unsaturated nitriles, amides, and ketones. Thus, the Michael reaction of pyrrolidine to these α,β-unsaturated compounds in the presence of solid $LiClO_4$ gave the corresponding Michael adducts in high yield and in a short time. The results and conditions are summarized in Table 2. On the other hand, in the case of α,β-unsaturated aldehydes, such as cinnamaldehydes, 1,2-addition is preferred and aminals were obtained exclusively.

In conclusion, we have developed a new method for accelerating the Michael reaction of amines with α,β-unsaturated olefins by using the inexpensive reagent $LiClO_4$. Although $LiClO_4$ is relatively cheap in comparison with many other Lewis acids used for these transformations, due to stability of $LiClO_4$ in water, it is possible to recover it by simple filtration and use it again after reactivating it by heating in vacuum at 160 °C. We believe that, these are improved conditions the Michael additions. The present procedure provides an efficient and general methodology for the preparation of β-amino esters, ketones and nitriles.

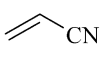
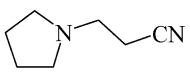
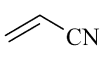
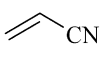
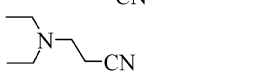
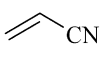
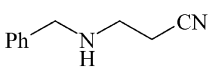
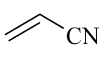
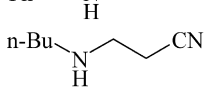
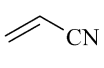
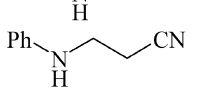
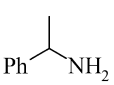
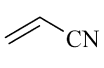
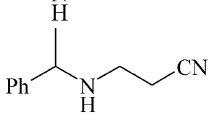
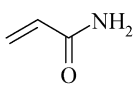
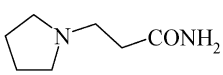
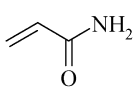
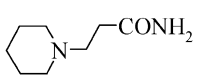
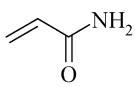
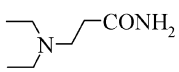
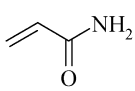
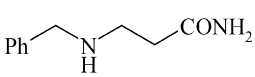
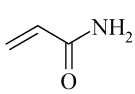
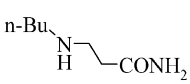
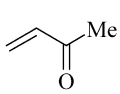
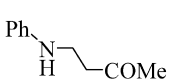


R = H, Ph; R' = CH_3; X = CN, $CONH_2$, COOMe, COMe

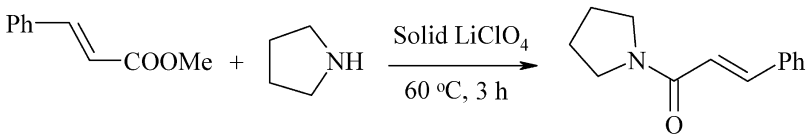


Scheme 1.

Table 2. Micheal addition of amines to α,β-unsaturated esters under solvent-free condition

Entry	Amines	Ethylenic compound	Product	Yield (%)[a] (time, h)[b])
1				82 (1)[4b]
2				80 (1)[4b]
3				83 (2)[1b]
4	$PhCH_2NH_2$			90 (2)[1b]
5	*n*-$BuNH_2$			93 (2)[1b]
6	$PhNH_2$			28 (4)[1a]
7				84 (2)[1a]
8				84 (1)[1c]
9				80 (1)[1c]
10				82 (2)[1c]
11	$PhCH_2NH_2$			76 (2)[1a]
12	*n*-$BuNH_2$			78 (2)[1a]
13[c]	$PhNH_2$			95 (1)[1b]

[a] Isolated yields.
[b] References.
[c] Only 20 mol% of solid $LiClO_4$ was used.



Scheme 2.

2. Experimental

2.1. General

NMR spectra were recorded on a Bruker ACF 500. IR spectra were measured using a Perkin–Elmer 1600 FTIR spectrometer. Column chromatography was performed on silica gel, Merck grade 60. CH_2Cl_2 was distilled before use. All reactions were performed under argon. Anhydrous $LiClO_4$ and other chemicals were purchased from Fluka or Merck.

Caution. Although we did not have any accident while using or drying $LiClO_4$, it is advisable to dry lithium perchlorate in hood using suitable lab-shield.

2.2. General procedure for the preparation of the Michael reaction of amines with α,β-unsaturated olefins

To a mixture of $LiClO_4$ (2 mmol) and methyl acrylate (2 mmol) was added pyrrolidine (3 mmol) and was stirred at room temperature under an argon atmosphere for 1 h. After completion of the reaction, CH_2Cl_2 (10 mL) was added, and $LiClO_4$ was removed by filtration. The solvent was evaporated and the product was isolated in almost pure from. Further purification was carried out by short column chromatography on silica gel eluting with ethyl acetate/petroleum ether. All compounds were characterized by retention times in GC and on the basis of their spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature.

2.2.1. Methyl 3-pyrrolidinyl-propionate. See Table 1, entry 1.[4f]

2.2.2. Methyl 3-piperidinyl-propionate. See Table 1, entry 2.[4f]

2.2.3. Methyl 3-(*N*,*N*-diethylamino)-propionate. See Table 1, entry 3.[4f]

2.2.4. Methyl 3-(*N*-benzylamino)-propionate. See Table 1, entry 4.[4f]

2.2.5. Methyl 3-(*N*-buthylamino)-propionate. See Table 1, entry 5.[1b]

2.2.6. Methyl 3-(*N*-phenylamino)-propionate. See Table 1, entry 6.[1b]

2.2.7. Methyl 3-(1-phenylethylamino)-propionate. See Table 1, entry 7.[1a]

2.2.8. Methyl 3-phenyl-3-pyrrolidinylpropionate. See Table 1, entry 8.[4f]

2.2.9. Methyl 3-phenyl-3-(*N*-buthylamino)-propionate. See Table 1, entry 10.[4f]

2.2.10. Methyl 2-methyl-3-pyrrolidinylpropionate. See Table 1, entry 11.[1b]

2.2.11. Methyl 2-methyl-3-(*N*,*N*-diethylamino)propionate. See Table 1, entry 13.[1b]

2.2.12. 3-Pyrrolidinyl-propionitrile. See Table 2, entry 1.[4b]

2.2.13. 3-(*N*,*N*-Diethylamino)-propionitrile. See Table 1, entry 3.[1b]

2.2.14. 3-(*N*-Buthylamino)-propionitril. See Table 1, entry 5.[1a]

2.2.15. 3-Pyrrolidinylpropionamide. See Table 2, entry 8.[1c]

2.2.16. 3-(*N*,*N*-Diethylamino)-propionamide. See Table 2, entry 10.[1c]

2.2.17. 4-(*N*-Phenylamino)-2-butanone. See Table 2, entry 13.[1b]

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