$LiClO_4$ CATALYZED AZA-MICHAEL ADDITION OF SECONDARY AMINES TO α,β-UNSATURATED ESTERS UNDER A SOLVENT-FREE CONDITION

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Received: 15 June 2016; Accepted for publication: 29 October 2016

ABSTRACT

An efficient aza-Michael addition of secondary amines to some α,β-unsaturated esters has been carried out using $LiCLO_4$ as a catalyst. β-amino esters were obtained in high yields at room temperature without using solvent.

Keywords: aza-Michael reaction, secondary amines, α,β-unsaturated esters, β-amino esters.

1. INTRODUCTION

The Michael reaction and its modified form such as aza-Michael, thio-Michael and carba-Michael reaction are among the most exploited reactions in organic chemistry [1]. Aza-Michael reaction products such as β-amino esters/ketones/nitriles are useful synthons for the preparation of several nitrogen containing bioactive natural products [2], antibiotics [3], and chiral auxiliaries [4]. Because a large number of biologically active compounds contain β-amino-ketone or ester moiety [5], the development of novel methodologies for the preparation of these compounds is an attractive area of research in synthetic organic chemistry.

The conjugate addition of a nitrogen nucleophile to an α,β-unsaturated ester leads to the formation of a β-amino ester [6]. β-Amino esters are not only building units of biologically important natural products including β-lactams but also versatile nitrogen-containing intermediates for compounds such as β-amino alcohol, β-aminoacids, β-lactam antibiotics, and 1,2-diamines [7].The conjugate addition of nitrogen nucleophiles to an unsaturated system requires either basic or acidic catalysts [8]. Lewis acid catalysts, such as $SnCl_4$, $AlCl_3$, or $TiCl_4$ [9], have been employed to effect this addition, but their use in stoichiometric amounts often cause severe environmental problems.

As a result of our continuing interest in studying the Michael reaction under solvent free and environmentally benign conditions, herein we report a process at room temperature using

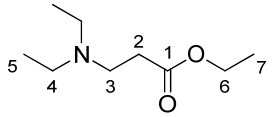
$LiClO_4$ as catalyst for the Michael addition of some secondary amines. The process is mild, easy to perform and gives excellent yield.

2. EXPERIMENTS

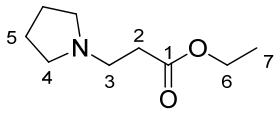
All reactions were monitored by thin-layer chromatography (TLC) using silicagel (Merck, 60–120 mesh). Column chromatography was performed using Merck silica gel (40-63 μm) packed by the slurry method, under a positive pressure of air. The ^1H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^1H NMR running at 500 MHz and ^{13}C NMR running at 125 MHz). The $CDCl_3$ was used as the NMR solvent unless otherwise stated. All products were characterized by comparison of their ^1H NMR and ^{13}C NMR spectra with those of in literature.The starting chemicals were obtained from commercial suppliers and used without further purification.

General procedure for aza-Michael addition: a mixture of α,β-unsaturated ester (10 mmol), amine (11 mmol, 1.1 equiv) and $LiClO_4$ (106.5 mg, 1.0 mmol, 0.1 equiv.) were stirred at room temperature for three days. The excess of organic components then were evaporated *in vacuo*. All products were purified by column chromatography and their structures were confirmed by ^1H NMR and ^{13}C NMR.

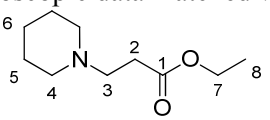
Ethyl 3-(diethylamino)propanoate:Colourless liquid. The^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (q, *J* = 7.0 Hz, 2H, H6), 2.72 (t, *J* = 7.5 Hz, 2H, H3), 2.44 (q, *J* = 7.0 Hz, 4H, H4), 2.36 (t, *J* = 7.5 Hz, 2H, H2), 1.18 (t, *J* = 7.0 Hz, 3H, H7), 0.95 (t, *J* = 7.0 Hz, 6H, H5). The^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8 (C1), 60.2 (C6), 48.1 (C3), 46.8 (C4), 32.4 (C2), 14.1 (C7), 11.9 (C5). NMR spectroscopic data matched with the published data [10].



Ethyl 3-(pyrrolidin-1-yl)propanoate:Colourless liquid. The ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.0 Hz, 2H, H6), 2.74 (t, *J* = 7.5 Hz, 2H, H3), 2.52-2.47 (m, 6H, H4 and H2), 1.77-1.72 (m, 4H, H5), 1.23 (t, *J* = 7.0 Hz, 3H, H7). The^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C1), 60.3 (C6), 54.0 (C4), 51.4 (C3), 34.2 (C2), 23.5 (C5), 14.2 (C7). NMR spectroscopic data matched with the published data [10].

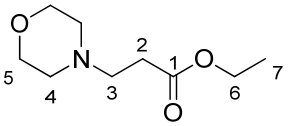


Ethyl 3-(piperidin-1-yl)propanoate: Colourless liquid. The ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.0 Hz, 2H, H7), 2.64 (t, *J* = 7.5 Hz, 2H, H3), 2.47 (t, *J* = 7.5 Hz, 2H, H2), 2.40-2.33 (m, 4H, H4), 1.59 – 1.52 (m, 4H, H5), 1.44-1.37 (m, 2H, H6), 1.23 (t, *J* = 7.0 Hz, 3H, H8). The^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (C1), 60.2 (C7), 54.2 (C3), 54.1 (C4), 32.3 (C2), 25.9 (C5), 24.3 (C6), 14.2 (C8). NMR spectroscopic data matched with the published data [11].

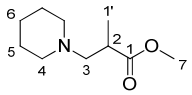


Ethyl 3-morpholinopropanoate: Colourless liquid. The ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.0 Hz, 2H, H6), 3.67-3.62 (m, 4H, H5), 2.64 (t, *J* = 7.0 Hz, 2H, H3), 2.47-2.39 (m, 6H, H4 and H2), 1.21 (t, *J* = 7.0 Hz, 3H, H7). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3 (C1), 66.9

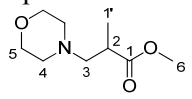
(C5), 60.3 (C6), 53.9 (C3), 53.3 (C4), 32.1 (C2), 14.2 (C7). NMR spectroscopic data matched with the published data [10].



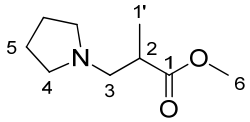
Methyl 2-methyl-3-(piperidin-1-yl)propanoate: Colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H, H7), 2.73 – 2.63 (m, 1H, H2), 2.59 (dd, *J* = 12.0, 8.5 Hz, 1H, H3), 2.38 – 2.24 (m, 5H, H4 and H2), 1.56 – 1.47 (m, 4H, H5), 1.38 (t, *J* = 5.0 Hz, 2H, H6), 1.12 (d, *J* = 7.0 Hz, 3H, H1'). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7 (C1), 62.4 (C3), 54.6 (C4), 51.4 (C7), 37.9 (C2), 26.0 (C5), 24.4 (C6), 15.7 (C1'). NMR spectroscopic data matched with the published data [11].



Methyl 2-methyl-3-morpholinopropanoate: Colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 3H, H6), 3.65 – 3.61 (m, 3H, H5), 2.71 – 2.64 (m, 1H, H2), 2.61 (dd, *J* = 12.0, 9.0 Hz, 1H, H3), 2.48 – 2.32 (m, 4H, H4), 2.27 (dd, *J* = 12.0, 6.0 Hz, 1H, H3), 1.12 (d, *J* = 7.0 Hz, 3H, H1'). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3 (C1), 67.0 (C5), 62.0 (C3), 53.7 (4), 51.5 (C6), 37.5 (C2), 15.4 (C1'). NMR spectroscopic data matched with the published data [10].

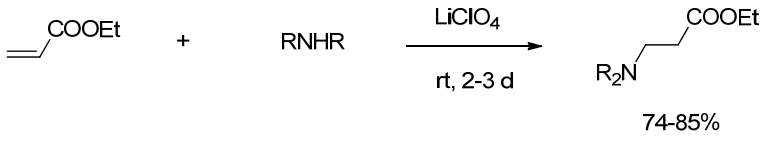


Methyl 2-methyl-3-(pyrrolidin-1-yl)propanoate: Colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H, H6), 2.77 (dd, *J* = 11.5, 8.5 Hz, 1H, H3), 2.71 – 2.62 (m, 1H, H2), 2.53-2.37 (m, 5H, H2 và H4), 1.74 (m, 4H, H5), 1.17 (d, *J* = 7.0 Hz, 3H, H1'). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6 (C1), 59.6 (C3), 54.2 (C4), 51.6 (C6), 39.6 (C2), 23.5 (C5), 15.8 (C1'). NMR spectroscopic data matched with the published data [10].



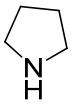
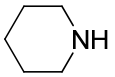
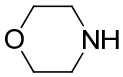
3. RESULTS AND DISCUSSION

In our study we did not employ primary amines to avoid double addition, which could lead to a mixture of products.At first, we examined the reaction of pyrolidine with ethyl acrylate and 10 % mole of $LiClO_4$ at room temperature in CH_2Cl_2. The reaction was not complete after three days (TLC analysis). Then the reaction was carried out under solvent-free condition. Partial conversion took place within 1 day, leading toaza-Michael reaction adduct. Complete conversion was observed in 3 days. We then continued reactions between diethylamine, piperidine and morpholine andethyl acrylate at the same conditions. After 2-3 d, the reactions were completed with very good yields of the Michael adducts (Scheme 1).The results are shown in the Table 1.

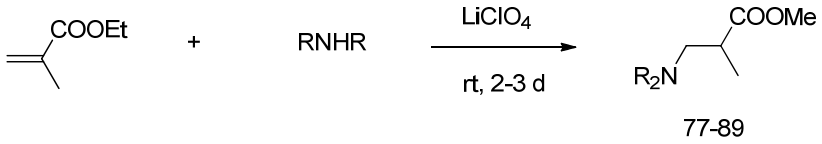


Scheme 1. Aza-Michael addition of secondary amine to ethyl acrylate.

Table 1. Aza-Michael addition of secondary amine to ethyl acrylate.

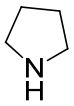
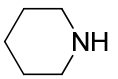
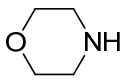
Reaction	Amines	Time (Days)	Yield (%)
1	$(C_2H_5)_2NH$	2	85
2		2	89
3		2.5	98
4		3	81

Finally, we carried out the aza-Michael addition between pyrolidine, piperidine and morpholine and methylmetacrylate at the same conditions described above (Scheme 2). The results were shown in Table 2.



Scheme 2. Aza-Michael addition of secondary amine to methylmetacrylate.

Table 2. Aza-Michael addition of secondary amine to methylmetacrylate.

Reaction	Amines	Time (Days)	Yield (%)
5		2	76
6		2.5	85
7		3	81

4. CONCLUSION

Seven aza-Michael reactions between selected secondary amines and ethylacrylate as well as methylmetacrylate using $LiCLO_4$ as catalyst were carried out with high yields. This is the first time theaza-Michael addition with this catalyst was carried out under solvent free conditions.

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TÓM TẮT

PHẢN ỨNG CỘNG AZA- MICHAEL CỦA MỘT SỐ AMIN BẬC HAI VÀO α,β-ESTERS KHÔNG NO SỬ DỤNG XÚC TÁC $LiCLO_4$ TRONG ĐIỀU KIỆN KHÔNG DUNG MÔI

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Phản ứng cộng aza-Michael của amin bậc hai vào α,β-este không nođã được thực hiện với xúc tác $LiClO_4$ ở nhiệt độ thường và trong điều kiện không dung môi. Các β-amino este thu được với hiệu suất cao.

Từ khóa: phản ứng aza-Michael, amin bậc hai, α,β-este không no, β-amino este.