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$LiCO_4/Et_3N$: Highly efficient and active catalyst for selective Michael addition of active methylene compounds under solvent-free condition

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ABSTRACT

A simple catalyst $LiClO_4/Et_3N$ has been developed and demonstrated to efficiently catalyze Michael addition reactions of active methylene compounds to conjugated ketones, nitriles, esters and nitroalkenes with remarkably high yields and in short reaction time. The Michael addition to nitroalkenes and α,β-unsaturated ketones proceeds quantitatively in the usual way, giving the *mono*addition product.

1. Introduction

The Michael reaction is generally regarded as one of the most efficient carbon–carbon bond forming reactions and can be easily applied to compounds having different functional groups [1]. Apart from its versatile applications in synthetic organic chemistry [2], it has found multiple industrial applications [3,4]. This reaction is industrially catalyzed by liquid [5–10] or solid [11–16] bases and remarkable progress has been made recently in developing new methodology for Michael addition and various catalysts [17–24,4,25–28]. However, there are various drawbacks with the reported methodologies such as long reaction times, use of halogenated solvents, difficulty in recovery of high boiling solvents, high temperatures, requirement of special efforts to prepare catalysts, use of costly catalysts, and moderate yields. Although transition metal-catalyzed Michael addition in organic solvent and water have been developed with a great deal of success, catalytic efficiency, substrate scope and reaction rate have been limited so far.

In our continuing studies on Michael addition reaction under solvent-free conditions and in the presence of $LiClO_4$ [29–37], herein we report a very mild, easy, and catalytic process for Michael addition of active methylene compounds at room temperature in quantitative yields.

2. Results and discussion

2.1. Catalytic activity

The effect of catalyst on the yield of Michael addition reaction is given in Tables 1–3. As shown in these tables, both reactivity and selectivity were strongly influenced by the catalyst. The reaction was best carried out by using one equivalent of diethyl malonate and one equivalent of chalcone in the presence of 5 mol% $LiClO_4$ and 1 mol% Et_3N, under solvent-free conditions for 5 min at room temperature. The crude product was isolated after washing with water and Michael type products were obtained in 97% yield. Both $LiClO_4$ and Et_3N were required for high reactivity at room temperature. Et_3N alone promoted the reaction, albeit a lower yield after 24 h, and in the presence of $LiClO_4$ alone, only a trace amount of the desired adduct was observed after long reaction time. Without using $LiCO_4$ and Et_3N no reaction was observed. Furthermore, in the organic solvents such as CH_2Cl_2, CH_3CN and 5 M solution of $LiClO_4$ in diethyl ether (LPDE), a large excess of catalyst was needed to give the desire product after a long reaction time. When the reaction was carried out under solvent-free condition, very small amount of catalyst was needed for the completion of the reaction. This interesting difference in behavior of 5 M LPDE and solid $LiClO_4$ is referred to the Lewis acidity (hard acid) of the lithium ion. In a coordinating solvent such as diethyl ether, the Lewis acidity of lithium ion is moderated and lower than under a solvent-less condition (Scheme 1).

With optimized reaction conditions in hand, the scope of the reaction was explored with different substances. Fortunately,

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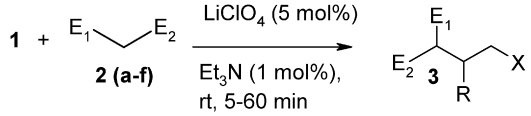
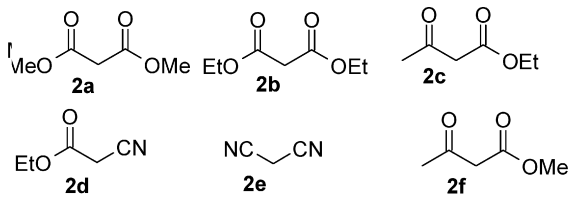
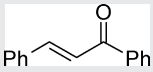
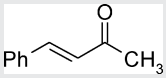
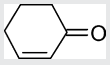
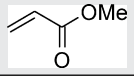
Table 1
Reaction of active methylene group with Michael acceptos

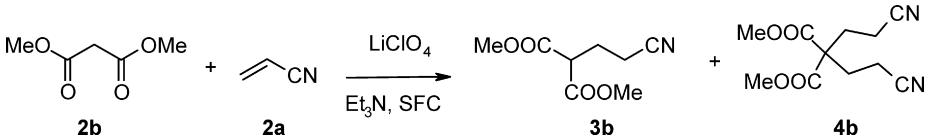




Entry	Michael donor	Michael acceptor, **1**	Time (min)	Yield (%)
1	**2a**		5	97
2	**2b**		5	97
3	**2c**		10	95
4	**2d**		10	90
5	**2e**		10	92
6	**2f**		10	90
7	**2a**		30	97
8	**2b**		30	95
9	**2c**		30	92
10	**2d**		45	92
11	**2f**		30	88
12	**2a**		60	97
13	**2b**		60	97
14	**2d**		60	97
15	**2f**		60	92
16	**2a**		45	90
17	**2b**		45	80
18	**2d**		45	82
19	**2a**		120	00 (90)[a,b]
20	**2b**		120	00 (90[a,b]
21	**2a**		1200	83[c]
22	**2a**		120	00 (93)[a,b]
23	**2b**		120	00 (92)[a,b]
24	**2a**		1200	80[c]

[a] Bis-adduct products.
[b] 5 mmole acrylonitrile and methylacrylate were used.
[c] reaction run at −15 °C.

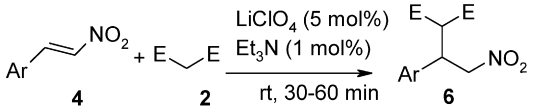
Table 2
Selective Michael addition under different reaction conditions

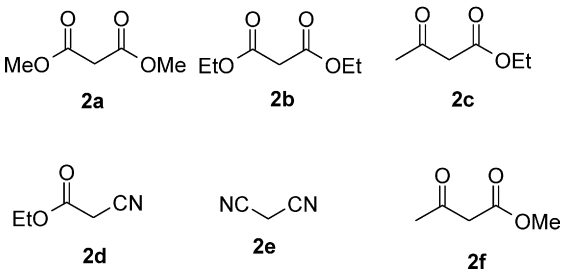


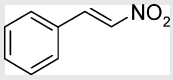
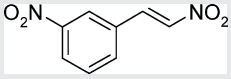
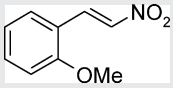
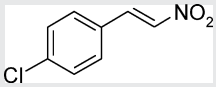
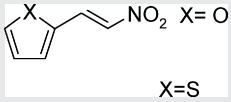
Entry	**1b** (mmol)	**2a** (mmol)	$LiClO_4$ (mmol)	Et_3N (μL)	Time (h)	Temperature (°C)	Yields (%)[a]	
							3b	**4b**
1	4	4	1	100	2	rt	0	85
2	4	2	1	100	2	rt	5	75
3	4	8	1	100	2	rt	0	90
4	4	8	1	100	2	0	60	30
5	4	8	4	–	50	−5 °C–rt	–	–
6	4	8	–	400	24	−5 °C–rt	–	30
7	4	8	0.5	100	2	−5 °C–rt	–	80
8	4	8	0.3	10	4	−10 °C–rt	66	33
9	10	22	0.3	5	20	−15 °C–rt	80	10

[a] The ratio was determined by ^{1}HNMR. Yields are based on starting material.

Table 3
Michael reacrion of nitroolefines

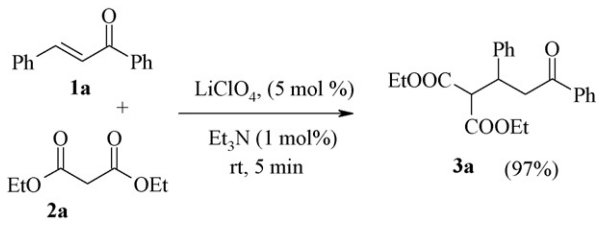




Entry	Michael donor	Michael acceptor	Time (min)	Yield (%)
1	**2a**		30	97
2	**2b**		30	92
3	**2c**		30	90
4	**2d**		50	92
5	**2e**([a]		50	95
6	**2f**		60	90
6	**2a**([a]		50	95
7	**2b**		60	82
8	**2c**		60	85
9	**2d**([a]		60	92
10	**2f**		60	95
11	**2a**		60	90
12	**2b**		60	88
13	**2d**		60	92
14	**2a**		60	90
15	**2c**		60	92
16	**2f**		60	88
17	**2b**		60	95
18	**2c**		50	95
19	**2f**		50	93
20	**2a**		50	86
21	**2b**		60	88

[a] 0.3 CH_2Cl_2 was added.

these results proved to be quite general and a wide range of structurally different compounds with active methylene group underwent Michael addition to various Michael acceptors such as α,β-unsaturated ketones, esters, nitriles and nitroolefins affording the corresponding products in quantitative yield. Methyl acrylate, cyclohexenone, methyl vinyl ketone, chalcone and benzylideneacetone underwent 1,4-addition with a wide range of active methylene compounds such as dimethyl malonate, diethyl malonate, ethyl cyanoacetate, malononitrile, ethyl acetoacetate and methyl acetoacetate in the presence of 5 mol% of lithium perchlorate under solvent-free conditions at room temperature to give the corresponding *mono*addition products in high yields. The results are summarized in Table 1.



Scheme 1.

However, in the case of methyl acrylate and acrylonitrile the reaction suffers from restriction caused by competing *mono* versus *bis* addition. The reaction at room temperature gave the *bis* adducts in high yields. On the other hand, many attempts have been made to produce *mono* addition products by changing the ratio of reactants, performing the reactions at different temperatures, and using different amine as catalysts. Finally, it was found that the reaction at −15 °C proceeded very slowly to give the *mono* adducts as the major product (Table 2).

Finally, the high reactivity of 1,3-dicarbonyl compounds in the $LiClO_4$ catalyzed reactions prompted us to investigate Michael addition of nitroolefins. Under the optimized conditions, a variety of nitroolefins with different structures were investigated, and the results are summarized in Table 3. Various styrene-type nitroolefins reacted smoothly with active methylene compounds in quantitative yields at room temperature. Generally, substituents on the benzene ring slightly influenced the reaction time as well as the yields. Nitroolefins bearing both electron-withdrawing and

electron-donating aryl groups gave the desired products in excellent yields.

These reactions were completed in short reaction times (5–120 min, depending on the substrates). This methodology is compatible with various α,β-unsaturated ketones, esters, nitriles, nitroolefins and different active methylene compounds under mild reaction conditions. No byproduct formation was observed. Moreover, the reactions are clean with nearly quantitative yields and with shorter reaction times in compared to other conventional methods.

3. Conclusion

We have developed an operationally simple and very mild process for Michael addition of active methylene compounds in the presence of $LiClO_4$/Et_3N catalyst. These reactions can be carried out in a very simple manner, just by mixing the substrates with a very small amount of catalyst. The high reactivity of the catalyst and simplicity of the work-up procedure together with high purity and short reaction time, without the use of any organic solvent in most cases, provide a straightforward and practical process for Michael reaction.

4. Experimental

4.1. General

Caution: Although we did not have any accident while using or drying $LiClO_4$, it is advisable to work in a fume hood using a suitable lab-shield.

All chemicals were obtained from commercial suppliers and used without further purification. Anhydrous conditions are not required for the reaction. NMR spectra were recorded on a Bruker ACF 500 using $CDCl_3/CCl_4$ or $CDCl_3$/DMSO-d_6 as solvent. Column chromatography was performed on silica gel, Merck grade 60. Ethyl acetate, petroleum ether and other solvent were distilled before use.

4.2. General procedure for Michael addition to enones and nitroalkenes

A mixture of a Michael acceptor (3 mmol), active methylene compound (3.2 mmol), $LiClO_4$ (0.02 g) and Et_3N (0.005 mL) was stirred at room temperature. Then the product was washed with water to give the crude Michael products with sufficient purity. In some cases the product was purified by column chromatography by using silica-gel and ethyl acetate and petroleum ether as eluent.

4.2.1. Selected spectroscopic data

Table 1, Entry 1: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 3.46 (dd, J = 8.2, 4.1 Hz, 1H), 3.55 (s, 3H), 3.62 (dd, J = 8.7, 4.2 Hz, 1H), 3.76 (s, 3H), 3.84 (d, J = 8.6 Hz, 1H), 4.17–4.21 (m, 1H), 7.18–7.28 (m, 5H), 7.44–7.56 (m, 3H), 7.93 (dd, J = 8.4, 1.2 Hz).

Table 1, Entry 12: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 2.14 (s, 3H), 2.21 (q, J = 7.2 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 3.41 (t, J = 7.3 Hz, 1H), 3.73 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 22.8, 29.9, 40.7, 50.6, 52.9, 169.8, 207.4.

Table 1, Entry 19: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 2.30 (t, J = 7.3 Hz, 4H), 2.50 (t, J = 7.3 Hz, 4H), 3.85 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 13.5, 30.2, 53.7, 118.8, 169.9.

Table 1, Entry 20: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.28 (t, J = 7.2 Hz, 6H), 2.25 (t, J = 7.9 Hz, 2H), 2.46 (t, J = 7.9 Hz, 2H), 4.27 (q, J = 7.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 13.4, 14.5, 29.9, 56.0, 60.7, 119.0, 169.5.

Table 2, Compound **3b** ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 2.23 (q, J = 7.3 Hz, 2H), 2.50 (t, J = 7.3 Hz, 2H), 3.54 (t, J = 7.3 Hz, 1H), 3.85 (s, 6 H); ^{13}C NMR(125 MHz, $CDCl_3/CCl_4$) δ 15.4, 24.9, 50.1, 53.8, 118.8, 168.9.

Table 3, Entry 1: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 3.76 (s, 3H), 3.77 (s, 3H), 3.88 (d, J = 9.1 Hz, 1H), 4.23–4.27 (m, 1H), 4.87–4.95 (m, 1H), 7.24–7.35 (m, 5H), ^{13}C NMR(125 MHz, $CDCl_3/CCl_4$) δ = 41.5, 43.3, 52.9, 55.1, 128.2, 128.8, 129.4, 136.5, 167.3, 167.8.

Table 3, Entry 3: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.02 (t, J = 7.2 Hz, 3H), 2.03 (s, 3H), 4.00 (d, J = 9.1 Hz, 1H), 4.15–4.25 (m, 2H), 4.70 (d, J = 6.2 Hz, 1H), 4.72–4.80 (m, 2H), 7.24–7.35 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 14.1, 30.4, 42.1,61.1, 62.7, 78.3, 128.2, 128.6, 129.4, 136.6, 167.1, 167.3, 200.2.

Table 3, Entry 2: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.30 (t, J = 6.8 Hz, 6H), 3.79 (d, J = 9.1 Hz, 1H), 4.03 (q, J = 6.8 Hz, 4H), 4.17–4.26 (m, 1H), 4.82–4.92 (m, 2H), 7.23–7.33 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 14.1, 14.5, 43.3, 55.1, 61.4, 62.1, 77.7, 128.4, 129.1, 136.9, 166.3, 167.4.

Table 3, Entry 15: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.09 (t, J = 7.2 Hz, 3H), 2.07 (s, 3H), 3.90–4.27 (m, 4H), 4.62–4.84 (m, 2H), 7.17 (d, J = 6.8 Hz, 2H), 7.32 (d, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 14.1, 30.2, 30.5, 41.4, 61.4, 62.4, 77.8, 129.1, 129.5, 134.4, 135.2, 166.6, 200.6.

Table 3, Entry 17: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.22–1.31 (m, 6H), 3.85 (d, J = 7.7 Hz, 1H), 4.12–4.32 (m, 5H), 4.82–4.85 (m, 2H), 6.20–6.28 (m, 2H), 7.30–7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 14.3, 37.1, 53.1, 62.1, 75.5, 108.6, 110.8, 142.8, 150.2, 166.8.

Table 3, Entry 16: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 2.18 (s, 3H), 3.81 (s, 3H), 4.00 (d, J = 9.8 Hz, 1H), 4.12–4.23 (m, 1H), 4.74–4.82 (m, 2H), 7.18 (d, J = 6.8 Hz, 2H), 7.33 (d, J = 6.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 30.5, 42.2, 53.2, 61.6, 129.6, 129.7, 134.8, 135.4, 167.9, 199.3.

Table 3, Entry 18: ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.25 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 4.06–4.22 (m, 4H), 4.78–4.80 (m, 2H), 6.16 (d, J = 1H), 6.26–6.30 (m, 1H), 7.31–7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 14.4, 30.3, 36.6, 59.7, 61.6, 62.4, 75.8, 76.0, 108.6, 110.9, 142.9, 150.1, 167.3, 201.0.

Table 3, Entry 20; ^{1}H NMR (500 MHz, $CDCl_3/CCl_4$) δ = 1.26 (t, J = 7.2 Hz, 6H), 3.29 (d, J = 7.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 4H), 4.86–4.88 (m, 2H), 6.89–6.93 (m, 2H), 7.12–7.29 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3/CCl_4$) δ = 14.1, 38.7, 55.7, 62.2, 78.2, 125.7, 127.0, 127.2, 139.1, 166.7, 167.2.

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