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Michael additions of primary and secondary amines to acrylonitrile catalyzed by lipases

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ABSTRACT

The present Letter details our findings on the lipase-catalyzed Michael reactions between primary or secondary amines and acrylonitrile. Several lipases were evaluated, and good results were obtained leading to the formation of Michael adducts in shorter reaction times than the uncatalyzed reactions.

1. Introduction

The use of enzymes for organic synthesis has become an emerging area for organic chemists. During the recent years, many enzymes have demonstrated high activity against nonnatural substrates in organic media and have become widely used for synthetic transformations such as reductions, oxidations, epoxidations, and aldol reactions, among others.[1–5] Lipases are the most used and well-known enzymes, which have high stability and activity, and can be used for different kinds of transformations.

In connection with our continuous work on synthetic applications of enzymes,[6] we start evaluating lipase catalytic activities of commercial enzymes on Michael addition reactions between secondary and primary amines and acrylonitrile (Scheme 1).

The literature points out that lipases are able to catalyze aminolysis and ammonolysis reactions[7–9], and the use of these enzymes on Michael addition reactions has been reported.[10]

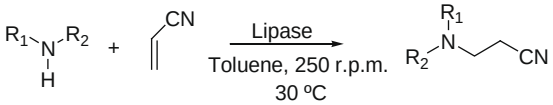
Gotor reviewed the non-conventional hydrolase chemistry, and disclosed some undesired Michael reactions that could occur competitively to aminolysis of esters. Ishida and Kato proposed a general mechanism to serine protease reactions[11] that act similarly to lipases.

In the case of the reaction of amines with alpha, beta-unsaturated esters, the competitive aminolysis would play a role and the final product selectivity pattern will be the result of three competitive processes, the aminolysis (the expected lipase-catalyzed reaction), the uncatalyzed Michael reaction and the unexpected catalyzed Michael reaction.

In the case of acrylonitriles, only two processes are possible, the catalyzed and the uncatalyzed Michael reactions which we choose to investigate.

Our group is studying the mechanism of the hydrolysis reaction and the geometry of the oxyanion hole that stabilizes the intermediate,[12] considering a late transition state.

Taking into account the model that was proposed early[11] and our own[12], in the latter step after the conjugated addition of the nucleophile, the zwiterionic intermediate is formed and is stabilized by both the oxyanion hole and the His–Asp pair.[11] We hypothesized, however, that this kind of mechanism in the Michael reaction based on a late transition state would not play a role to justify rate acceleration effects (in Michael additions),[13] that is, in the case of esters, the transition states would be very similar in both Michael and aminolysis, considering the oxyanion formation, so not justifying a rate acceleration effect toward the desired Michael product.



Scheme 1. Michael addition reaction.

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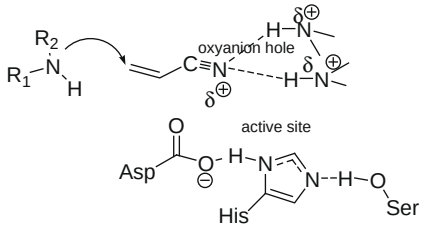

Figure 1. Hypothesized mechanism for the lipase-catalyzed Michael addition.

Table 1
Michael reaction between primary and secondary amines and acrylonitrile without the use of lipase catalyst

Entry	Amine	Time (h)	Conversion[a]
1	Benzylamine (**1**)	2	**6**, 92%
2	Diethylamine (**2**)	3	**7**, 83%
3	Diisopropylamine (**3**)	3	**8**, 74%
4	Pyrrolidine (**4**)	2.5	**9**, 72%

[a] Based on GC analysis.

So we envisaged that in the lipases'-catalyzed Michael reactions, substrate activation would occur via protonation (or high energy hydrogen bonding) of the nitrile so implying in a substrate activation that would result in a rate acceleration effect (Fig. 1).

Based on this expectation, we undertook the present investigation on the Michael reaction between primary and secondary amines (**1**–**4**) and acrylonitrile (**5**) envisaging a kind of substrate activation.

To compare such expectation, we carried out Michael reaction without the use of lipase as catalyst. The results displayed in Table 1 show that all amines lead to the formation of Michael addition product in 2–3 h.

To investigate the effect of lipase catalyst on this type of reaction, we decided to perform the same reaction in the presence of different types of lipases, and the results are summarized in Table 2.

As shown in Table 2, all lipases evaluated led to a consistent shorter reaction time tendency (about 50% time reduction) when compared to the same reaction without the use of the lipase catalyst. Novozyme 435 (Table 2, entries 1, 5, 9, and 13) gave the best results, but the other systems were also effective.

In conclusion, it has been demonstrated that different lipases that share in general the same active site are capable to catalyze the Michael reaction between primary or secondary amines and acrylonitrile. In comparison with the non-catalyzed reaction, this methodology leads to a great improvement in the reaction time. Studies are in progress to observe if enantioselectivity can be achieved with beta-substituted acrylates or acrylonitriles and also on the kinetics of these reactions.

2. Experimental

Reactions were carried out using amine (1 mmol), acrylonitrile (1 mmol), and 2% w/w of Lipase, in toluene (5 mL). The reaction was monitored by GC until the reaction finished. Structures of all substances were confirmed by comparison with NMR data and GC-MS analysis, and are included in the supplementary data.

Table 2
Michael reaction between primary and secondary amines and acrylonitrile in the presence of a lipase catalyst

Entry	Amine	Lipase	Time (h)	Conversion[a]
1	**1**	Novozyme 435	0.8	**6**, 90%
2	**1**	Lipozyme TL IM	1	**6**, 88%
3	**1**	Lipozyme RM IM	1	**6**, 92%
4	**1**	PS Amano	1	**6**, 85%
5	**2**	Novozyme 435	1.2	**7**, 80%
6	**2**	Lipozyme TL IM	1.2	**7**, 85%
7	**2**	Lipozyme RM IM	1.2	**7**, 71%
8	**2**	PS Amano	0.8	**7**, 77%
9	**3**	Novozyme 435	1.2	**8**, 70%
10	**3**	Lipozyme TL IM	1.4	**8**, 71%
11	**3**	Lipozyme RM IM	1.4	**8**, 65%
12	**3**	PS Amano	1.2	**8**, 68%
13	**4**	Novozyme 435	1.4	**9**, 71%
14	**4**	Lipozyme TL IM	1.6	**9**, 66%
15	**4**	Lipozyme RM IM	2	**9**, 61%
16	**4**	PS Amano	1.5	**9**, 70%

[a] Based on GC analysis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.100.

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