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The application of microwave irradiation to the Michael synthesis of esters of -amino acids

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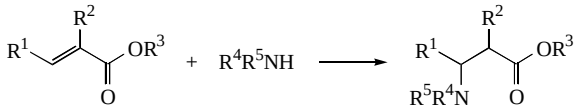
Microwave irradiation accelerates the Michael 1,4-addition of primary and cyclic secondary amines to esters of , -unsaturated -unsubstituted carboxylic acids.

The occurrence of -amino acids in natural products such as alkaloids and antibiotics has always attracted the attention of organic chemists. This is indicated by the increasing activity of research in the field of synthesis of -amino acids or their esters.

The addition of amines to the double bond of esters of acrylic acids is a principal and very facile method for the synthesis of -amino acid esters.



This version of the Michael reaction usually requires activation[1] (prolonged boiling[2,3] or high pressures[4]).

Recently it has been shown[5,6] that highly oxophilic lanthanide triflates accelerate the Michael reaction and make it possible to conduct it at room temperature during several hours.

Our recent studies[7] have confirmed the efficiency of ytterbium and samarium triflates as catalysts for the Michael conjugate addition. In fact, the nucleophilic addition of primary and cyclic secondary amines to esters of methacrylic, crotonic and cinnamic acids occurs at room temperature in satisfactory yields (up to 79%); a diastereoisomeric excess (d.e.) equal to 14–28% is achieved only in some cases.

In this work we propose accelerating the Michael reaction by microwave irradiation (MI). This method has begun to be used in organic synthesis only in the last decade[8–11] and is applied for the first time to the Michael synthesis of -amino esters.

The reactions of esters of , -unsaturated acids with a 1.5-fold excess of amines were carried out without a solvent in a commercial microwave oven (Funai MO785VT) in a reaction vessel for several minutes. The power of MI depends on the stability of the starting compounds under MI conditions. The Michael adduct was separated from the unreacted starting substances by column chromatography on silica gel with a hexane–ethyl acetate mixture (2:1) as the eluent. It should be noted especially that no side products or products of polymerisation of the initial esters were found in all cases.

The results of nucleophilic addition of morpholine to the double bond of methyl cinnamate under various conditions (Table 1, entries 1–3) show that 60 min of MI leads to the formation of the corresponding methyl -amino- -phenyl-propionate in a chemical yield of 31%, whereas the yield of this ester obtained after stirring the reactants for 12 days at room temperature with a catalytic quantity of ytterbium triflate was only 4% and that without a catalyst was less than 1%.

A similar dependence was observed for methyl and *sec*-butyl crotonates: the use of MI makes it possible to reach considerably higher yields of Michael reaction products over shorter periods than the catalytic activation by ytterbium triflate (entries 4–17). The simultaneous use of MI and ytterbium triflate does not change the chemical yield of the target -amino ester.

It should be emphasised especially that quite a different picture was observed when esters of methacrylic acid were used as the substrates in the Michael reaction. The microwave treatment unlike the ytterbium triflate (entries 18–23) does not activate the conjugate addition in this case. The methyl ester of tiglic acid also does not yield any substantial amount of the 1,4-addition product. To elucidate the reasons for this finding, special investigation is needed.

Apparently, the chemical yield of -amino esters in the above cases depends on the presence of substituents in the - and -positions and on the nature of these substituents.

Analysis of the data presented in Table 1 indicates that the bulky phenyl group in methyl cinnamate reduces the chemical yield of the 1,4-addition product compared to the yield attained when a methyl group occurs in the same position (in the crotonate, entries 3 and 17). The presence of a methyl substituent in the -position with respect to the carbonyl group prevents the formation of amino esters under MI. The structure and nucleophilicity of the amine also exerts an important influence on the chemical yield of -amino esters in the MI-activated Michael reaction. For example, more nucleophilic cyclic secondary amines (piperidine and morpholine) react with crotonates to give products in higher yields than primary amines (entries 13, 14 and 17). Benzylamine, which is sterically less hindered, gives the target -amino ester in a higher yield than -phenylethylamine (entries 5 and 7; 9 and 11). Ethyl -amino- -phenylacetate, , ′-diphenylethylamine and anabasine, which are even more sterically hindered and less nucleophilic, do not react with crotonic acid esters under these conditions.

The 1,4-addition of amines to crotonates and cinnamates results in the formation of a new asymmetric centre at the C atom of the ester. The use of chiral -phenylethylamine in this reaction leads to asymmetric induction and, hence, to the formation of mixtures of diastereoisomeric racemates with a slight diastereoisomeric excess (7% d.e., entry 7, 9% d.e., entry 11,† 16% d.e., entry 6, 18% d.e., entry 10†). Optically inactive *sec*-butyl crotonate reacts with benzylamine (entries 8 and 9), piperidine (entries 12–14) and morpholine (entries 15–17) to give 1:1 diastereoisomeric mixtures of the corresponding -amino esters.

Thus, microwave irradiation can serve as an effective and convenient method for the synthesis of -unsubstituted -amino esters by the Michael reaction.

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† Excess of one pair of the two pairs of diastereoisomeric racemates.

Table 1 Reactions of esters of acrylic acids with amines.

	R^1	R^2	R^3	R^4	R^5	Time	Catalyst	Yield[a] (%)
1	Ph	H	Me	$-(CH_2)_2O(CH_2)_2-$		12 days	–	<1
2	Ph	H	Me	$-(CH_2)_2O(CH_2)_2-$		12 days	$Yb(OTf)_3$	4
3	Ph	H	Me	$-(CH_2)_2O(CH_2)_2-$		60 min	MI[b]	31
4	Me	H	Me	$PhCH_2$	H	4 days	$Yb(OTf)_3$	46
5	Me	H	Me	$PhCH_2$	H	10 min	MI[b]	53
6	Me	H	Me	PhCHMe	H	7 days	$Yb(OTf)_3$	11
7	Me	H	Me	PhCHMe	H	10 min	MI[b]	34
8	Me	H	Bu^s	$PhCH_2$	H	7 days	$Yb(OTf)_3$	44
9	Me	H	Bu^s	$PhCH_2$	H	18 min	MI[b]	74
10	Me	H	Bu^s	PhCHMe	H	7 days	$Yb(OTf)_3$	12
11	Me	H	Bu^s	PhCHMe	H	10 min	MI[b]	55
12	Me	H	Bu^s	$-(CH_2)_5-$		6 days	$Yb(OTf)_3$	50
13	Me	H	Bu^s	$-(CH_2)_5-$		10 min	MI[b]	84
14	Me	H	Bu^s	$-(CH_2)_5-$		10 min	MI[c]	64
15	Me	H	Bu^s	$-(CH_2)_2O(CH_2)_2-$		5 days	–	17
16	Me	H	Bu^s	$-(CH_2)_2O(CH_2)_2-$		9 days	$Yb(OTf)_3$	60
17	Me	H	Bu^s	$-(CH_2)_2O(CH_2)_2-$		25 min	MI[d]	72
18	H	Me	Me	$PhCH_2$	H	6 days	$Yb(OTf)_3$	16
19	H	Me	Me	$PhCH_2$	H	10 min	MI[d]	3
20	H	Me	Me	PhCHMe	H	4 days	$Yb(OTf)_3$	1
21	H	Me	Me	PhCHMe	H	50 min	MI[b]	2
22	H	Me	Bu^n	PhCHMe	H	10 days	$Yb(OTf)_3$	15
23	H	Me	Bu^n	PhCHMe	H	17 min	MI[d]	<1

[a]All the yields refer to isolated chromatographically pure compounds. All the structures were confirmed by ^1H NMR (400 MHz) and IR spectroscopy data. [b]The power of MI was 850 W. [c]The power of MI was 170 W. [d]The power of MI was 510 W.

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