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Comparative Study of Physical and Chemical Activation Modes. The Case of the Synthesis of β-Amino Derivatives.

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Abstract : The activation of the conjugate addition of amines to α,β-ethylenic substrates is considered. Pressure (physical parameter) is a powerful tool to promote the reaction due to its effect on the nucleophilic attack on the double bond of the acrylic compound with development of zwitterionic species. Combination of pressure and lanthanide catalysis (chemical activation) is a highly efficient multiactivation mode, though it is unable to operate in strongly congested systems. Physicochemical activation by water considerably promotes the synthesis of β-amino derivatives. However in the case of acrylic esters, it is of little value since the β-aminoesters formed undergo rapid retro-Michael reactions. Copyright © 1996 Elsevier Science Ltd

Introduction :

Activation of reactions has been a permanent central point in organic chemistry, since the ability to optimize the yield of an organic synthesis rests on appropriate activation methods. Activation can be made in several ways which may be roughly ranked into four categories (physical, chemical, physicochemical, biochemical). Among physical methods, temperature was the earliest to be used due to its simplicity. In the last decades, intensive efforts have been made concerning new modes of activation.[1] Physical activation can also be achieved by means of high pressure, which has proved useful in many aspects,[2] particularly to force sterically congested systems to reactivity.[3] Catalysis (chemical activation) is nowadays frequently used mainly either *via* Lewis acids or transition metals. A more recent activation mode considers special reaction media (physicochemical activation) such as LPDE ($LiClO_4$-diethyl ether),[4] ammonium nitrate,[5]... and water.[6] Organic reactions in aqueous media are increasingly studied, since it became rapidly evident that reactions characterized by negative activation volumes are also accelerated in water.[7]

The aim of the present study is at comparing the synthetic advantages of the following activation methods[8] used either individually or in combination (multiactivation) :

- pressure (physical parameter)
- lanthanide catalysis (chemical parameter)
- use of water (physicochemical parameter).

The reaction selected for the purpose is the conjugate addition of amines to α,β-ethylenic derivatives to yield β-amino compounds. Such additions belong to the class of Michael reactions. They are well-known chemical processes whose kinetics have been studied in detail.[9]

Table 1. Conjugate addition of amines to α,β-ethylenic compounds.
Effect of pressure, catalyst and water on yields (%)[a]

Entry	Acrylic compound			amine		T (°C)	Pressure (MPa) no catalyst		Pressure (MPa) with catalyst[b]		Water[c]
	R_3	R_4	X	R_1	R_2		0.1	300	0.1	300	0.1
1	H	H	CO_2Me	iPr	Me	50	0	13	17	80	0
2	Me	H	CO_2Me	iPr	iPr	50	2	55	6	61	0
3	Me	H	CO_2Me	tBu	H	30	2	23	6	65	0
4	H	Me	CO_2Me	tBu	H	30	0	11	4	47	0
5	H	Me	CO_2Me	iPr	Me	50	0	28	10	50	0
6	H	H	CN	$-(CH_2)_5-$		20	95	-	-	-	100
7	H	H	CN	mepip[e]		30	16	100	-	-	73
8	H	H	CN	dimepip[e]		30	0	0	-	0	0
9	H	H	CN	tBu	H	30	~0	62	35	100	98
10	H	H	CN	iPr	Me	30	32	100	-	100	100
11	H	H	CN	iBu	iBu	30	0	11	20	91	40
12	H	H	CN	iPr	iPr	50	0	8	2	95	69
13	H	H	CN	C_6H_{11}	C_6H_{11}	50	0	7	5	68	10
14	H	H	CN	Ph_2CH	H	50	0	5	6	51	28
15	H	H	CN	Ph	Ph	50	-	0	-	0	0

16	H	Me	CN	tBu	H	50	-	0	-	0	40
17	H	Me	CN	iPr	Me	50	-	0	0	3	72
18	H	Me	CN	- $(CH_2)_5$ -		20	1	19	5	36	100
19	H	Me	CN	Pr	Pr	50	0	2	0	7	19
20	H	Me	CN	iPr	iPr	50	-	0	-	0	0
21	Me	H	CN	tBu	H	30	0	0	0	0	6
22	Me	H	CN	iPr	Me	30	0	0	-	5	50
23	Me	H	CN	- $(CH_2)_5$ -		20	2	15	18	86	95
24	H	H	$CONH_2$	tBu	H	30	10	51	4	-	12
25	H	H	$CONH_2$	iPr	Me	20	20	85	21	100	35
26	H	H	$CONH_2$	- $(CH_2)_5$ -		20	90	100	-	-	52
27	H	H	$CONH_2$	Pr	Pr	20	12	67	64	83	96
28	H	Me	$CONH_2$	tBu	H	30	-	-	-	-	0
29	H	Me	$CONH_2$	tBu	H	50	0	1	0	11	11
30	H	Me	$CONH_2$	iPr	Me	30	0	1	0	5	20
31	H	Me	$CONH_2$	- $(CH_2)_5$ -		20	2	12	17	65	70
32	H	H	COMe	tBu	H	20	65	46[d]	28[d]	(d)	54[d]

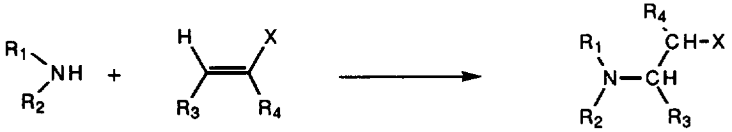
a : acrylic compound (1 mmol), amine (1-1.5 mmol), acetonitrile (1 mL), reaction time (24 h). Under the conditions indicated, the reactions are fully selective, meaning that the Michael adduct is formed as unique product (see however, footnote d).

b : ytterbium triflate (2 mol %) in acetonitrile.

c : water (3.5 mL)

d : polymerisation (exclusive or in addition to the Michael adduct).

e : mepip (2-methylpiperidine), dimepip (2,6-dimethylpiperidine).



Such compounds deserve high interest as some of them are important intermediates in organic synthesis (β-aminoesters for example[10]). Simple primary unbulky amines usually react with unsubstituted acrylic compounds without special activation. However, the reactivity is considerably depressed upon increasing the bulk and/or changing the position of alkyl or phenyl groups in both the amine and the α,β-ethylenic compound.[11,12] In order to stimulate reactivity, we have considered the effect of pressure, the effect of a lanthanide catalyst and the effect of water.

Results :

In a previous paper, it was shown that the addition of amines to α,β-ethylenic esters was significantly promoted by pressure, particularly when crowded substrates were involved.[12] Combination of pressure and lanthanide catalysis permitted to extend the reaction to the synthesis of highly congested β-aminoesters.[13] In the present article, we examine the Michael reaction of unsaturated (Table 1) :

- esters (entries 1-5)
- nitriles : acrylonitrile (entries 6-15), methacrylonitrile (entries 16-20), crotononitrile (entries 21-23)
- amides : acrylamide (entries 24-27), methacrylamide (entries 28-31)

with primary and secondary amines substituted with alkyl groups of various size in order to compare the feasibility of the reactions with those previously studied with acrylic esters.

- unsaturated ketones were initially considered as other candidates. However under conditions of Table 1, the addition of amines to methyl vinyl ketone is prone to polymerization (entry 32 in Table 1).

The results are recorded in Table 1 listing the yields of β-amino products obtained respectively at 0.1 and 300 MPa pressure (about 1 and 3000 bar) (no catalyst added), at 0.1 and 300 MPa (upon addition of the lanthanide catalyst) and finally the yields obtained with water as the medium at 0.1 MPa (no catalyst added). Following observations can be made.

1. The effect of pressure :

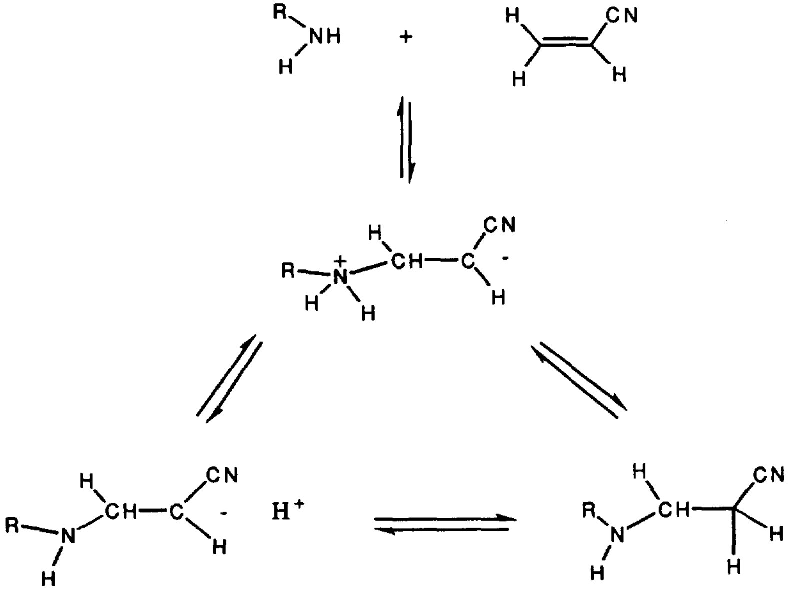
The effect of pressure in the uncatalyzed reaction is remarkable, particularly when acrylic esters or nitriles are involved. Whereas all amines under consideration are unreactive at ambient pressure (with the notable exception of piperidine and its α-methyl substituted analog (entries 6, 7), β-aminonitriles are obtained in low to moderate yields at 300 MPa. The use of a higher pressure should greatly improve the yield as it was observed in the addition of amines to acrylates.[13] This is verified : for example, the uncatalyzed reaction depicted in entry 11 affords a 75 % yield at 900 MPa. The α- and β-methyl substituted acrylonitriles are much less reactive than their unsubstituted analog. However, here again, when a reference yield is available at atmospheric pressure an increase of pressure is highly beneficial for the reaction (entries 18, 23).

Acrylamide is more reactive than acrylonitrile under ambient conditions. The pressure effect is also very perceptible albeit apparently to a lesser extent (cf. entry 24 vs entry 9). Methacrylamide like methacrylonitrile is unreactive even under pressure, at least with the amines considered.

In order to get a quantitative idea of the pressure effect, the kinetics of the addition of isopropylamine (a reaction not listed in Table 1) and t-butylamine to acrylonitrile have been followed at distinct pressures (Table 2). As for acrylate additions the reactions examined follow second-order kinetics.

Table 2. Kinetic effect of pressure in the addition of amines to acrylonitrile (in acetonitrile at 34.0° C).

Pressure (MPa)	10^6 k (l.M^{-1}.s^{-1}) isopropylamine	Pressure (MPa)	10^6 k (l.M^{-1}.s^{-1}) t-butylamine
1.5	3.22	0.1	0.72
5.5	3.57	3	0.80
10	4.28	7	0.84
22	5.38	10	0.90
46	7.76	12	0.92
58	9.08	21	1.30
72	10.62	45	1.63
		69	2.25
		120	3.85



Scheme 1. Mechanism

Plotting ln k against pressure enables the determination of the activation volume. The corresponding $\Delta V^{\neq}$ - values (± 5 cm^3.mol^{-1}) are ~ -65 cm^3.mol^{-1} for the isopropylamine addition and

~ -60 $cm^3.mol^{-1}$ for the t-butylamine reaction. These extraordinarily negative values confirm the huge pressure acceleration of such Michael reactions. They refer to a mechanism similar to that one characterizing the corresponding reactions with acrylic esters[11] (scheme 1). The rate-determining step is a nucleophilic attack on the activated double bond with complete development of a zwitterionic species which undergoes rapid proton transfer.[14] The very large negative value of $\Delta V^{\neq}$ is indicative of a highly ordered and late transition state and considerable electrostriction due to the generation of the zwitterion concentrated on the cyano group.[11] The above activation volumes are even higher (in absolute value) than the $\Delta V^{\neq}$ - values previously determined for the conjugate addition of amines to acrylic esters. In the latter case, there is presumably some delocalization of the negative charge spread on the two oxygen atoms of the ester group.

2. The catalytic effect of lanthanides :

Lanthanide complexes possess coordination properties which are effective for site selectivity.[15] Their catalytic properties are related to the specific coordination number and stereochemistry of lanthanide (III) compounds.[16] Generally, the preferred binding sites are those with donor groups containing negatively charged oxygen atoms (keto, carboxylate groups). Moreover, the ability of catalytic amounts of lanthanides to activate coordinating nitriles[17] as well as imines[18] has also been recognized.

Among lanthanide compounds, ytterbium triflate is a potent Lewis acid catalyst due to the electron-withdrawing trifluoromethanesulfonyl group which increases the acidity[19] and ytterbium whose organic derivatives have one of the strongest Lewis acidity in the lanthanide series.[15]

In this article as shown in Table 1, soluble lanthanide compounds work as effective Lewis acid catalysts in Michael reactions,[20] particularly in the addition of amines to acrylic esters in the same way as outlined in our previous work.[13] Two series of experiments using ytterbium trifluoromethanesulfonate as the catalyst have been carried out at ambient and 300 MPa pressure respectively. Like in the ester reactions, acrylic nitriles lead to analogous results as exemplified in Table 1. As for pressure, the presence of the catalyst allows reactions to take place where otherwise no reactivity can be detected (entries 9, 11-14, 18, 23). Combination of pressure and lanthanide catalysis is highly beneficial for those reactions. The most representative example is provided in entry 9 : whereas t-butylamine does not add to acrylonitrile at normal pressure under conditions of Table 1, ytterbium triflate activates the reaction in such a way that it is completed at 300 MPa. Excellent yields are also achieved in other unsaturated nitrile additions by the multiactivation procedure, while no reaction occurs at 0.1 MPa in the respective uncatalyzed reactions (entries 11-14, 23).

The behavior of acrylamide in the catalyzed reaction is puzzling. The results shown in entry 27 (atmospheric pressure) are in full agreement with lanthanide catalysis, however, at 300 MPa the catalyst effect is not significant. In one case, there is no catalytic effect at all (entry 25) and even, the presence of ytterbium triflate can be detrimental (entry 24). At variance, lanthanide catalysis is evident in high pressure methacrylamide reactions (entries 29-31).

To sum up, the reactions shown in Table 1 indicate that ytterbium triflate is an active catalyst in Michael reactions involving unsaturated nitriles and amides with some restriction concerning acrylamide additions.

3. The water effect :

The use of water as a medium for organic reactions which normally require organic solvents has been widely developed since the discovery of rate acceleration in aqueous Diels-Alder cycloadditions during the last decade.[21] The cause of the often dramatic kinetic changes has been attributed to several factors : cohesive energy of water, hydrogen bonding, polarity, enforced hydrophobic interactions, micellar catalysis... In fact, based upon the observed effects in the numerous and various reactions investigated till now, there is no unique reason accomodating all results. It became obvious that the water effect depends on the properties of the reaction partners, particularly on the relative contribution of solvophobic and polarity parameters.[22] In one of our previous works, we could not detect any appreciable water effect in the addition of bulky amines to acrylic esters.[13] We have, therefore, also been interested in the behavior of unsaturated nitriles and amides towards amines in aqueous solution. The results listed in the last column of Table 1 are highly instructive :

- In the case of acrylic esters, no reaction at all is observed in agreement with our previous article[13] (entries 1-5)

- this is not the case when acrylic nitriles are involved. Except with amines substituted by highly congested groups (entries 8, 15), water is a favorable medium for the addition of amines to acrylonitrile. Entries 9, 11, 12 provide the most representative examples ; whereas at atmospheric pressure no reaction takes place when no catalyst is present, the yields reach 98, 40, 69 % respectively, even more than in the pressure uncatalyzed reaction (62, 11, 8 %). However, the yields obtained in the pressure catalyzed reaction are higher (100, 91, 95 %)

- the difference in reactivity under pressure catalytic and water conditions is even more dramatic in the reactions involving α or β methyl substituted acrylonitriles. Tertio-butylamine reacts only in aqueous solution (entries 16, 21). The reaction goes to completion with piperidine (entries 18, 23). For the other reactions, water is revealed as a very appropriate medium.

- in the case of acrylic amides, the water effect is not evident. The yields in the acrylamide series are generally lower than in the pressure uncatalyzed reactions (entries 24-26). In the case of methacrylamide, the addition is promoted in water when compared to the pressure uncatalyzed reaction. The aqueous behavior of both amides may possibly be ascribed to peculiar effects (solubility or other, vide infra and Table 4). Particularly, solubility effects should be taken into account. Most reactions investigated here involve heterogeneous conditions despite relatively low concentrations of substrates (3 - 4 x 10^{-3} M).

It should be pointed out that we also tested combination of ytterbium triflate and water in some of our reactions (entries 1, 2, 5, 9, 10, 11). No yield improvement was found compared to the yield in the corresponding aqueous reaction with no catalyst added.

The interpretation of these results can be assessed on the most recent views related to the water effect on organic reactions :

* Placed in an aqueous medium, organic substrates rearrange as aggregates in order to minimize unfavorable interactions between the apolar reactants and water. This is known as the hydrophobic effect. Engberts introduced the concept of "enforced" hydrophobic interactions meaning additional reduction of

the hydrophobic surface of the reaction accompanying the formation of the activated complex. This is certainly one of the reasons leading to rate acceleration.[23]

In a general way, organic syntheses are faced with the problem of reacting water-insoluble molecules. The poor solubility of hydrophobic molecules in water is ascribed to unfavorable entropy (unfavorable enthalpy was also advanced as the reason[24]). In water, the reaction proceeds via the small amounts of dissolved reactants. If the substrates, even one,[25] are totally insoluble, no reaction occurs in aqueous media. A limited solubility, even very low, is required.[26] Considering the results of Table 1, the higher yields obtained in aqueous acrylonitrile and methacrylonitrile additions could be due to increased hydrophobicity of the nitriles compared to acrylates and amides. However, the apparent absence of reactivity in the acrylic esters reactions cannot be caused by a non-solubility of the unsaturated esters in water, since the rate of Diels-Alder addition of cyclopentadiene with acrylates is enhanced in water.[27] In fact, the results relative to the aqueous acrylate-amine reactions are at first sight quite surprising. It seems of interest to check whether these reactions normally occuring under ambient pressure conditions with unbulky amines take place or not in water. The results listed in Table 3 show that water does not suppress the reaction, although it seemingly induces a significant rate depression (Table 3), contrary to expectation.

Table 3. Comparative yields of β-aminoesters obtained in the addition of n-propylamine to acrylates.

Acrylic ester	Yields (%)* in acetonitrile	Yields (%)* in water
methyl methacrylate	7	1.5
methyl crotonate	37	5

* : 30° C, 0.1 MPa, 24 h.

* Another possibility is connected with the hydrogen-bonding capacity of water[28] leading to polarization of the substituents of one of the substrates (in this work, $COOCH_3$, CN, $CONH_2$) in such a way that the activated complex might have a more polar character than in conventional solvents and would be, therefore, stabilized by hydrogen bonding.[29]

* Based upon the fact that reactions accelerated by pressure -showing thereby negative activation volumes $\Delta V^{\neq}$- are also those undergoing rate acceleration in water, the cohesive energy of water, acting like external pressure, was proposed as a possible cause for this acceleration. It tends to suppress any cavity in the water structure, so that the acceleration originates from steric compression of the transition state in a cavity of the water structure.[30]

If we take into account this proposal, the present Michael reactions should be considerably accelerated in aqueous solution in view of the high negative values of $\Delta V^{\neq}$, including the reactions of acrylic esters.

* One could envision a possible change of nucleophilicity of amine when transposing the system from an organic solvent to water. According to the mechanistic scheme 1, since the positive charge is necessarly locked on the nitrogen atom, the stability of the carbanion could govern the reactivity. Water may affect this stability. Under such consideration, the high yields of methacrylonitrile and crotononitrile

adducts obtained in aqueous solution could point to a significant larger build-up of charge in the activated complex. But again, this does not elucidate the results with the acrylic esters.

* It appears therefore that the apparent absence of rate acceleration in the aqueous addition of amines to acrylic esters is presumably related to the couple acrylate-amine. It should be reminded that the reaction of amines with α,β-unsaturated compounds can be reversible depending on conditions.[9c] In order to test possible reverse processes, we synthesized some β-amino compounds and examined their fate in acetonitrile and in water respectively under the same conditions as for the forward reaction (Table 4).

Table 4. Occurence of reverse reactions for β-amino compounds.

Amino compound	% residual amino compound after reaction in CH_3CN	 in water
(iPr)(Me)N-CH(Me)CH_2COOCH_3[a]	98	4
(iPr)(Me)N-CH(Me)CH_2CN[b]	100	100
$(CH_2)_5N$-$CH_2CH_2CONH_2$[c]	98	95

[a]: 50° C, 0.1 MPa, 24 h
[b]: 30° C, 0.1 MPa, 24 h
[c]: 20° C, 0.1 MPa, 24 h

Clearly, β-aminoesters undergo quick reversion to substrates in aqueous solution, whereas β-aminonitriles and β-aminoamides are stable or quasi stable. The zero yields of aminoesters in water are now understandable. In fact, there is no anomaly. Water accelerates the addition of amines to acrylic esters as it does for nitriles and amides. Simply, the adduct is not stable in aqueous solution undergoing elimination to the initial substrates.

Table 5. Simplified pictogram of the efficiency of various activation modes in the addition of amines to α,β-ethylenic compounds.

Compound	Pressure	Lanthanide catalysis	Water
acrylic, methacrylic crotonic esters	+++	++	-
acrylonitrile	+++	+++	++ to +++
methacrylonitrile	+++	++	+++
crotononitrile	+++	++	+++
acrylamide	++	++	+
methacrylamide	++	++	++

(-) means depressive effect due to reverse reaction
(+, ++, +++) denotes the magnitude of the promoting effect.

Conclusion :

The conjugate addition of amines to α,β-ethylenic substrates can be activated in several ways. Pressure is a powerful means to promote the reaction on account of the large negative activation volume. However, it is inoperant in cases where steric hindrance becomes prohibitive. Combination of pressure and lanthanide catalysis gives excellent results, except in some cases where the steric accessibility of the reaction centers is too hindered. Physicochemical activation by water is revealed as an exceptional method to stimulate reactivity, though it is not general. It is remarkable in the addition of amines to α,β-ethylenic nitriles, even superior to the two other activation modes used in this work, but has a detrimental effect in the corresponding acrylic ester reactions due to reverse reactions. Acrylamide reactions are not particularly promoted in aqueous solution. Table 5 roughly summarizes these effects.

The present article demonstrates that there is no unique efficient activation method to promote Michael reactions. The nature of the reaction partners dictates the choice of the activation parameter. However, up to now no general procedure is available to bring highly congested systems to reactivity. To this respect, multiactivation could show promise to be incorporated in the growing armory of activation methods.[31]

Experimental part :

Experiments are made with distilled acetonitrile and water. Amines and acrylic compounds are commercially available chemicals. Acrylic esters are distilled before use. Ytterbium trifluoromethanesulfonate is supplied by Fluka. The yields are determined by ^{1}H NMR spectroscopy (Brucker AC 200) with $CDCl_3$ or CD_3COCD_3 as solvents and TMS as internal standard from the relative intensities of characteristic protons (CH_3-N, CH_2-N, OCH_3 ...) of the Michael adduct vs methoxy groups of 1,2,3-trimethoxybenzene (internal standard in the appropriate run). In the case of acrylic esters, the aromatic protons of the internal standard are the reference. Pure adducts are readily obtained either by simple evaporation in vacuo or column chromatography.

High pressure experiments. In a typical run, trimethoxybenzene (about 0.07 mmol) is weighed and placed in a flexible PTFE tube (1 ml). Then acrylic compound (~ 1 mmol) and amine (1-1.5 mmol) are introduced via syringe and weighed. The tube is filled up with acetonitrile and placed into the thermoregulated high pressure vessel. After pressurization to 300 MPa for 24 h, the mixture is collected, acetonitrile and volatile substrates removed on rotary evaporation. The residue is analyzed by NMR spectroscopy.

Catalytic experiments. After weighing the required catalytic amount of ytterbium triflate (2 % molar), the same filling procedure is adopted as above. To remove the lanthanide catalyst after experiment, water is added to the reaction mixture and the organic layer extracted as below.

Experiments in water. The filling procedure is identical, however, the volume of the reaction tube is 3.5 ml. After reaction, dichloromethane is added to the aqueous mixture. The organic layer is collected by two successive extractions and dried. Final work-up follows as above.

Kinetic experiments are carried out in the same way as described in the previous work.[11]

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