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Ultrasound Irradiation Effects on the Asymmetric Michael Reaction

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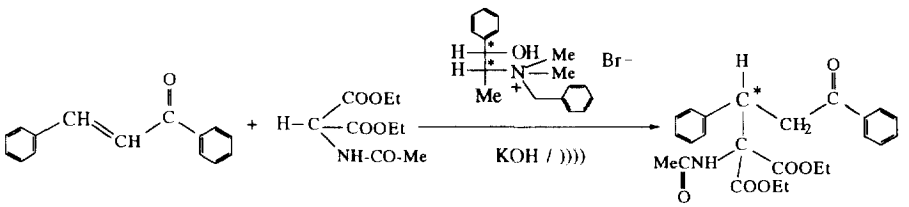
Abstract : Ultrasound irradiation enhances the rate and improves the yield of the heterogeneous asymmetric Michael reaction without any modification of the enantioselectivity with respect to standard procedure. These improvements are assigned to ultrasonic mechanical effects.

Catalytic asymmetric synthesis is the most attractive method for the preparation of pure enantiomers, using achiral starting materials. In conjugate addition reactions considerable induction has been found in the Michael reaction.[1-5] The chiral Michael addition of N-acetylaminomalonate to chalcone under PTC conditions without solvent using optically active tetraalkylammonium salts as catalysts was reported by some of us.[6] A major advantage of this method is the enhancement in chiral recognition in the absence of added organic solvent, rendering the system more rigid and decreasing the molecular motions. However, under these conditions, the chemical yields of the Michael adduct remained limited to 40-60 % with enantiomeric excess up to 82% in favour of the S or of R enantiomer according to catalyst chirality.[6b,d] The yield limitation can be due either to the viscosity of the reacting mixture (mass transfer problems) or/and to the reversibility of the Michael reaction. We have recently described the influence of sonication upon the Pudovik reactions, Michael-like reaction of labile P-H group with unsaturated compounds, involving radicalar or ionic mechanism as a function of the reagents and experimental conditions.[7] Here, we wish to report the effects of ultrasound irradiation on the yield and asymmetric induction of this heterogeneous asymmetric reaction (Reaction 1): since the sonication might improve the yield of the reaction by its physical effects (solid disruption, surface erosion and cleaning, improved mass transfer), we could dread that their chemical effects (single electron transfer, radicalar mechanism) involve a loss of the enantioselectivity.[8-12]



Reaction 1

1 **2** **3**

The reaction of chalcone **1** with malonate **2** in stoichiometric amounts (5 mmoles) in the presence of catalytic quantities (6 % mol) of base (KOH) and (-) N-benzyl N-methyl ephedrinium bromide[6d] occured at 60 °C either without solvent (molten **1** constitutes the liquid phase) or in the presence of toluene (3 mL) as solvent.

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In order to determine the influence of ultrasound, all experiments carried out under sonication were repeated under magnetical stirring at the same temperature. Enantiomeric excesses of the Michael adduct **3** were determined by NMR chiral shift using europium salts.[6a,d]

Effect of the Source of Ultrasound - A 20 kHz generator (Bioblock Vibracell 600 W) connected to either *i)* a direct immersion horn (Φ = 13 mm, power setting = 1.5) or *ii)* a cup horn (Φ = 60 mm, power setting = 5) was used. In the later case the reactor is a flat-bottomed flask dipped in contact with the horn, whereas in the former case, the reactor is a cylindrical round-bottomed flask. The presence of a liquid phase (solvent) is required when the immersion probe is used. The comparative study of magnetically stirred and sonicated Michael reaction in toluene at 40 °C after 5 minutes (Figure 1) clearly demonstrates the interest of sonication.

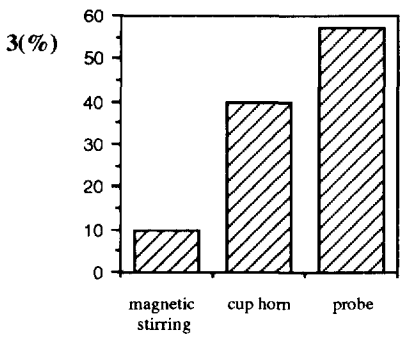

Figure 1 - Sonication effect upon the asymmetric Michael reaction.

The sonication enhances the rate of reaction *vs* conventional stirring by 4 times for the cup horn and more than 5 times for the probe. This enhancement is also observed when the reaction occured without solvent. However, ultrasound is less effective under "dry" conditions due to the high viscosity of the reaction mixture in the absence of the solvent.

Influence of the Temperature - When the Michael addition was carried out under sonication (probe) in toluene in a 20 - 80 °C temperature range for 5 minutes, the amount of **3** goes through a rather sharp maximum (58 % at 40 °C). At the same time, the enantioselectivity dramatically decreases (Figure 2).

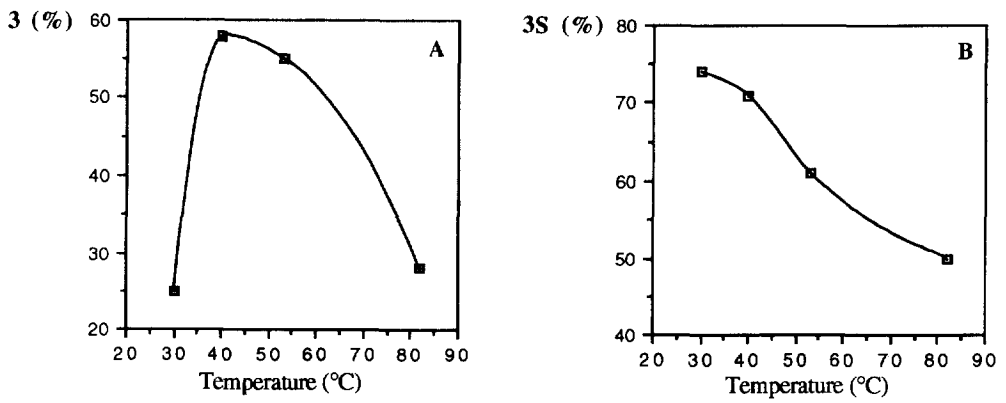

Figure 2 - Influence of the temperature upon the yield (A) and the enantioselectivity (B) of the asymmetric Michael reaction

Since the Michael addition is a reversible process, these data strongly suggest that the loss of selectivity and the decrease of the yield might be related to the retro-Michael reaction. In this hypothesis, what will be the effect of sonication on this reaction and could it be accelerate the Michael *vs* to the reverse reaction? Moreover, if the ultrasound irradiation can induce the generation of radicals (sonochemical effects), what will be its effects upon the enantioselectivity of the reaction?

When the progress of the Michael reaction was studied as a function of time (Figure 3), an increase of the reaction rate is observed under sonication *vs* classical stirring and this acceleration is more significant in the presence of solvent (45 % of **3** after 2 minutes of sonication instead of 12 % under magnetic stirring).The retro-Michael reaction realized in toluene from the purified adduct **3** as a enantiomeric mixture (S/R = 70/30) under the same conditions than the Michael reaction in the presence of dry powder of KOH and (-) N-methyl ephedrinium bromide shows the disappearing of **3** as a function of time (Figure 3). As the direct reaction, the rate of the reverse reaction is enhanced under sonication. So, for sonochemical reaction, the equilibrium was reached after about 30 minutes with disappearing of more than 50 % of **3** with simultaneously appearance of chalcone **1** and malonate **2**, but also a loss of enantioselectivity and the formation of a racemic mixture (S/R = 50/50).

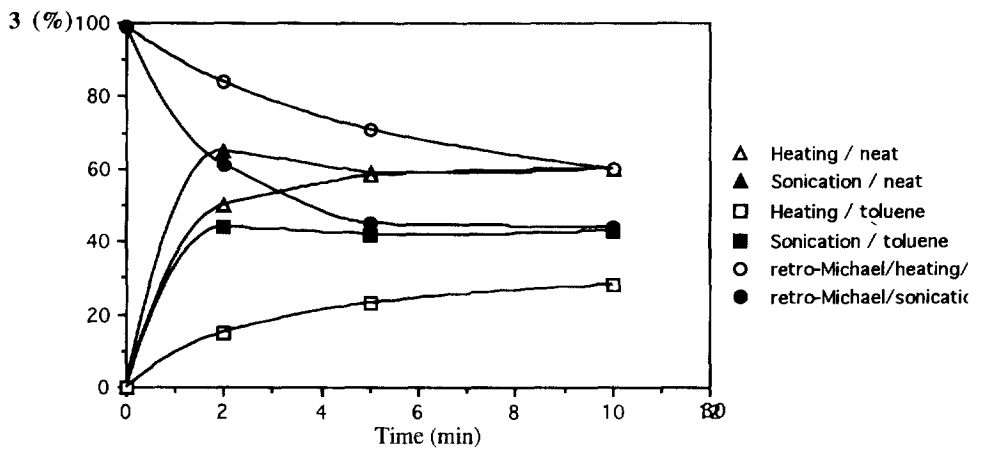

Figure 3- Influence of the reaction time on the progress of the Michael reaction in the presence of toluene or without solvent at 60 °C under sonication (cup horn) or magnetic stirring .

Consequently, the rate enhancement of Michael reaction under sonication in the presence of solvent is balanced with the retro-Michael reaction. On the other hand, the Michael reaction without solvent is accelerated under sonication without a noticeable loss of yield and enantioselectivity. When the reaction occured at 60 °C without solvent, chalcone **1** (m.p. = 59-60 °C) constitutes the liquid phase, and the formation of the Michael adduct **3** (m.p. = 110-112 °C) increases the heterogeneity of the mixture and the mass transfer problems. So, the use of 3 equivalents of chalcone must avoid these disadvantage and displaces the equilibrium in favour of the formation of **3**. Actually, the optimal conditions are reached when the reaction of 3 eq. of **1** with 1 eq. of **2** occured at 60 °C without solvent under sonication (cup horn) for 5 minutes, we observed a significant improvement of the reaction yield with formation of **3** in **82 % yield (isolated product)** in the same enantiomeric ratio (S/R = 70/30) than under magnetic stirring (Table 1).

In conclusion, ultrasound irradiation enhances the rate and improves the yield of the heterogeneous reaction by mechanical effects upon dispersion of the solid KOH and ammonium salt and homogenization of the mixture by reducing the mass transfer problems. The demonstration of the influence of the retro-Michael reaction upon the yield and the enantioselectivity of the reaction has allowed to determine the optimal conditions for this asymmetric Michael reaction : the ultrasound irradiation involving no loss of the enantioselectivity of the reaction, it intervenes only by its physical effects.

Table 1 - Chalcone stoichiometric effect upon the yield and the enantioselectivity of the Michael reaction without solvent at 60 °C for 5 minutes.

Activation method	**1** (eq)	**3** (%)*		S / R
		(a)	(b)	(%)
Sonication	1	59	50	70/30
(cup horn)	3	96	82	70/30
classical	1	58	50	70/30
heating	3	82	70	73/27

* Calculated from **2**

(a) Yield determined from ^{1}H NMR spectra. (b) Yield determined from isolated products

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