

The Effect of Microwave and Ultrasonic Irradiation on the Reactivity of Benzaldehydes under Al₂O₃, Ba(OH)₂, and K₂CO₃ Catalysis

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The solventless microwave reactions of substituted benzaldehydes with imidazole and piperidine on Al₂O₃ as an inorganic support resulted in the Cannizzaro reaction. The products of Cannizzaro reactions were also the main products at the attempted condensation reactions of benzaldehydes with vinyl acetate using barium hydroxide as the catalyst under microwave irradiation, but corresponding cinnamaldehydes were formed only under ultrasonic irradiation. 4-Chloro- and 4-bromobenzaldehydes proved to be unreactive at sonochemical S_NAr substitutions, but afforded S_NAr reactions under microwave irradiation.

The main reactions of substituted benzaldehydes are condensation reactions, redox reactions of the Cannizzaro and Tischenko type, Pinacol coupling, and in the case of 4-halosubstituted benzaldehydes, also S_NAr reactions. The accelerating ultrasound effect on the phase-transfer Cannizzaro reaction was described several years ago [1]. It is known that the Cannizzaro reaction undergoes sonocatalysis in a homogeneous solution or in a biphasic system in the presence of calcined barium hydroxide. The catalyst contains reducing and basic side and quantitative yields were obtained after only 5 min exposure to ultrasound [2]. We described recently [3] also a beneficial ultrasound effect on the S_NAr reactions of 4-fluorobenzaldehyde, but no other 4-halobenzaldehydes were examined. The beneficial effect of microwave irradiation on S_NAr as well as condensation reactions is well documented, too [4]. An interesting paper appeared recently [5] describing synthesis of substituted cinnamic aldehyde *via* condensation of benzaldehydes with vinyl acetate. The main drawback of this reaction was that long reaction time was necessary, in spite of the fact that a strong base C-200 was used as the catalyst. We decided to check the ultrasound and microwave effect on the S_NAr reactions of 4-halobenzaldehydes with some amines as well as on the reactions of benzaldehydes with vinyl acetate.

EXPERIMENTAL

All chemical reagents were commercially available.

The carbonyl compounds as well as amines were purified (distilled and crystallized, respectively) before application in the reactions. Basic Al₂O₃ (99 %, "100 mesh") and barium hydroxide were obtained from Aldrich; neutral Al₂O₃ 90 (Brockmann II—III) was obtained from Lachema, Brno.

All products were analyzed by ¹H NMR and GC-MS spectroscopy and the spectroscopic data were in accordance with those of commercial standards.

The ¹H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in CDCl₃ with tetramethylsilane as an internal standard. Melting points were determined on a Kofler hot stage. GC spectra were recorded on GC Trace 2000 Series instrument, mass spectra were recorded on Voyager spectrometer.

All sonochemical experiments were carried out in a glass reactor fitted to an ultrasonic horn ULTRAGEN (20 kHz, 300 W) under pulsed conditions (pulse length: 4 s, 50 % duty) for 15 min under an air atmosphere. The energy emission of the reactor was measured by the *Weissler* test [6]: under the conditions used, sonication of aqueous KI (50 cm³, 1 mol dm⁻³) for 3 min gave 4.6 × 10⁻⁶ mol dm⁻³ of KI₃. All microwave experiments were carried out in the SYN-THEWAVE 402, PROLABO reactor, power setting 180 W.

Classical S_NAr Reactions on 4-Halobenzaldehydes

Potassium carbonate (3.04 g; 0.022 mol) was

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Table 1. Results of the S_NAr Reactions of 4-Halobenzaldehydes Ia—Ic with Amines IIa, IIb

Run	Irradiation	Time min	X	Amine	Yield/% of IIIa, IIIb
1	Ultrasonic	15	F	Imidazole	75
2	Microwave $\theta_{\text{final}} = 194^{\circ}\text{C}$	5	F	Imidazole	95
3	Ultrasonic	15	Cl	Imidazole	0
4	Microwave $\theta_{\text{final}} = 178^{\circ}\text{C}$	5	Cl	Imidazole	39
4	Ultrasonic	15	Br	Imidazole	0
5	Ultrasonic	15	Br	Imidazole ^a	0
6	Ultrasonic	15	Br	Imidazole ^b	0
7	Microwave $\theta_{\text{final}} = 172^{\circ}\text{C}$	5	Br	Imidazole	30
8	Ultrasonic	15	F	Piperidine	85 (48 ^c)
9	Microwave $\theta_{\text{final}} = 169^{\circ}\text{C}$	5	F	Piperidine	63
10	Ultrasonic	15	Cl	Piperidine	0
11	Microwave $\theta_{\text{final}} = 168^{\circ}\text{C}$	5	Cl	Piperidine	3
12	Ultrasonic	15	Br	Piperidine	0
13	Microwave $\theta_{\text{final}} = 165^{\circ}\text{C}$	5	Br	Piperidine	8

a) Reaction was catalyzed with 0.5 mol of CuBr; b) reaction with 1 mol of KF; c) yield of classical reaction, thermal heating and stirring, 5 h.

Table 2. Cannizzaro Reaction of 4-Halobenzaldehydes Ia—Ic with Amines IIa, IIb under Microwave Irradiation

Run	X	Amine	θ_{final} °C	Conversion/% of Ia—Ic	Al ₂ O ₃
1	F	Imidazole	194	80	Neutral
2	Cl	Imidazole	151	95	Neutral
3	Br	Imidazole	153	87	Neutral
4	Br	Imidazole ^a	192	91	Neutral
5	Br	Imidazole ^b	30	0	—
6	Br	Imidazole ^c	76	0	—
7	Br	—	97	80	Neutral
8	Br	— ^a	132	95	Neutral
9	Br	Imidazole	98	80	Basic
10	Br	Imidazole ^d	20	0	Neutral
11	Cl	Piperidine	104	80	Neutral

a) Reaction with 1 mol of KF; b) reaction with 1 mol of K₂CO₃, without Al₂O₃; c) reaction with 1 mol of K₂CO₃, without Al₂O₃, in ethanol; d) 4-Bromobenzaldehyde and imidazole were ground together with Al₂O₃ in a mortar at room temperature for 30 min.

added to the solution of appropriate secondary cyclic amine (0.02 mol) and 4-halobenzaldehyde (0.2 mol) in DMSO (20 cm³). The reaction mixture was heated at 100 °C for 5 h. The reaction mixture was then poured into water (400 cm³) and the emulsion formed was extracted three times into diethyl ether (75 cm³). The ethereal solution was washed with water, dried over anhydrous Na₂SO₄, ether was distilled off on a rotary vacuum evaporator and the crude product was chromatographed on silica using isohexane—ethyl acetate ($\varphi_{\text{r}} = 9:1-2:1$) as the eluent.

Sonochemical S_NAr Reactions on 4-Halobenzaldehydes

Potassium carbonate (3.04 g; 0.022 mol) was added to the solution of appropriate secondary cyclic amine (0.02 mol) and 4-halobenzaldehyde (0.02 mol) in DMSO (20 cm³). The reaction mixture was sonicated

for 15 min. The temperature of the reaction mixture attained 150 °C at the end of sonication. The reaction mixture was cooled down to 60 °C and then poured into distilled water (400 cm³) and processed as described above.

Microwave S_NAr Reactions on 4-Halobenzaldehydes

Potassium carbonate (0.76 g; 0.0055 mol) was added to the solution of appropriate secondary cyclic amine (0.005 mol) and 4-halobenzaldehyde (0.005 mol) in DMSO (7.5 cm³). The reaction mixture was microwave-irradiated for 5 min or 10 min. The final temperatures of the reaction mixtures are given in Tables 1—3. The reaction mixture was cooled down to 60 °C and then poured into distilled water (100 cm³) and processed as described above.

Table 3. Results of the Reactions of 4-Halobenzaldehydes *Ia*, *Ib* with Vinyl Acetate *VI* under Microwave Irradiation

Run	Base	X	Solvent	Time	Conversion/% of <i>Ia</i> , <i>Ib</i>	Yield/% of <i>IVa</i> , <i>IVb</i>	Yield/% of <i>VIIa</i> , <i>VIIb</i>	Yield/% of <i>VIIIa</i> , <i>VIIIb</i>
				min				
1	Ba(OH) ₂ · 8H ₂ O	F	–	3	42 $\theta_{\text{final}} = 112^\circ\text{C}$	24	14	4
2	Ba(OH) ₂ · 8H ₂ O	Cl	–	2	90 $\theta_{\text{final}} = 109^\circ\text{C}$	77	< 1	0
3	Ba(OH) ₂ · 8H ₂ O	Cl	–	10	96 $\theta_{\text{final}} = 132^\circ\text{C}$	37	< 1	21
4	Ba(OH) ₂ · 0.7H ₂ O	Cl	–	5	4 $\theta_{\text{final}} = 86^\circ\text{C}$	0	4	0
5	Ba(OH) ₂ · 0.7H ₂ O	Cl	THF	5	4 $\theta_{\text{final}} = 70^\circ\text{C}$	0	4	0
6	Ba(OH) ₂ · 0.7H ₂ O	Cl	2-ClC ₆ H ₄ CH ₃	5	30 $\theta_{\text{final}} = 136^\circ\text{C}$	23	7	0
7	K ₂ CO ₃	Cl	–	10	0 $\theta_{\text{final}} = 110^\circ\text{C}$	0	0	0

Microwave Cannizzaro Reaction of 4-Halobenzaldehydes

4-Halobenzaldehyde (0.005 mol), amine (0.005 mol), and alumina (10 g) were ground together in a mortar and microwave-irradiated for 5 min without solvent. The final temperatures of the reaction mixtures are given in Table 2. The reaction mixture after cooling was suspended in ethyl acetate (30 cm³). Organic solutions were dried with Na₂SO₄ and ethyl acetate was evaporated to give crude 4-halobenzyl alcohols. Al₂O₃ was after drying poured in water and filtered to remove Al₂O₃. The filtrate was acidified to obtain 4-halobenzoic acids.

Microwave Reactions of 4-Halobenzaldehydes with Vinyl Acetate

A mixture of vinyl acetate (1.1 cm³, 0.012 mol), 4-halobenzaldehyde (0.01 mol), and Ba(OH)₂ · *x*_iH₂O (*x*₁ = 8; *x*₂ = 0.7) (0.012 mol) was microwave-irradiated for the time given in Table 3 without solvent or with THF (10 cm³) or 2-chlorotoluene (10 cm³) as the solvents. The reaction mixture after cooling down was poured in water (30 cm³) and filtered to remove the insoluble material. The filtrate was acidified to obtain 4-halobenzoic acid. The insoluble portion was suspended in chloroform (30 cm³). Organic solution was dried with Na₂SO₄ and chloroform was evaporated to give the mixture of 4-halobenzyl alcohol, 4-halobenzyl acetate, and 4-halocinnamaldehyde. The crude mixture was analyzed by GC-MS as well as by ¹H NMR spectroscopy. The products were isolated by column chromatography on SiO₂ using isohexane—ethyl acetate ($\varphi_r = 4:1$) as the eluent.

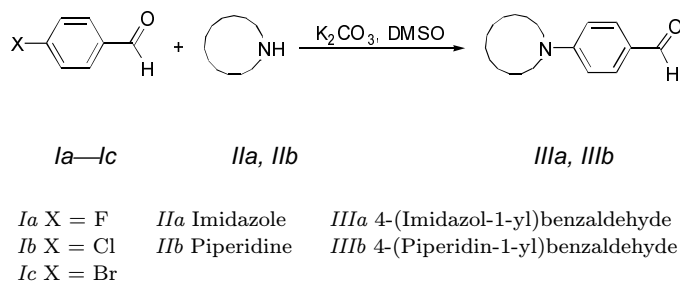
Sonochemical Reactions of 4-Halobenzaldehydes with Vinyl Acetate

A mixture of vinyl acetate (1.1 cm³, 0.012 mol) and 4-halobenzaldehyde (0.01 mol) in THF (10 cm³) was added to a suspension of Ba(OH)₂ · *x*_iH₂O (*x*₁ = 8; *x*₂ = 0.7) (0.012 mol) in THF (20 cm³). The reaction mixture was sonicated for 30 min. The reaction mixture was cooled during the irradiation in an ice bath and the temperature of the reaction mixture attained 20 °C at the end of sonication. The reaction mixture was then poured into cold water (30 cm³) and filtered to remove the insoluble barium salt. The filtrate was extracted with chloroform (2 × 20 cm³) and the organic layer was washed with water, dried with Na₂SO₄ and evaporated to obtain crude product which was chromatographed on silica using isohexane—ethyl acetate ($\varphi_r = 4:1$) as the eluent.

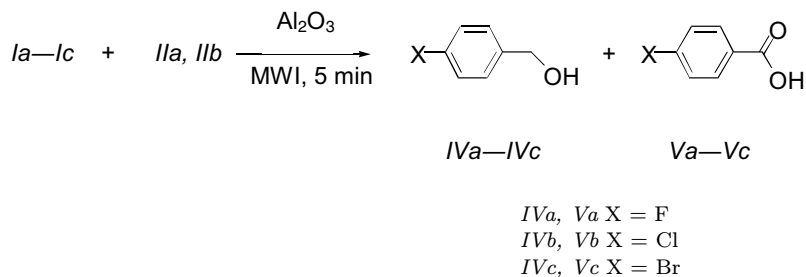
RESULTS AND DISCUSSION

In the previous study [3] we described a beneficial ultrasound effect on the nucleophilic aromatic substitutions on 4-fluorobenzaldehyde with different azacycloalkanes and azoles in dimethylsulfoxide under potassium carbonate catalysis. Reactions were clean and high yields of the products were isolated after 15 min sonication. In this study we found out that a drawback of the method was its limitation to 4-fluorobenzaldehyde only (Scheme 1). Other 4-halobenzaldehydes were inert in these S_NAr reactions (Table 1).

Sonochemical S_NAr reaction on 4-bromobenzaldehyde with imidazole gave no product even under catalysis with 0.5 mol of CuBr (Entry 5). Adams and Clark [7] described an excellent methodology for halogen ex-



Scheme 1



Scheme 2

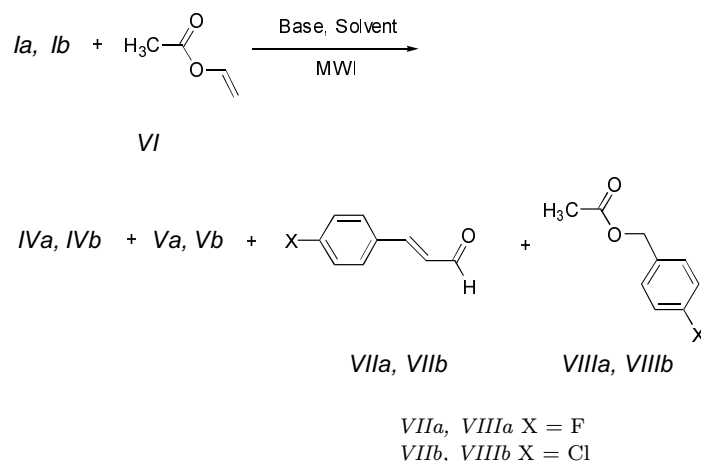
change on aromatics. A halogen group is displaced by a fluoride ion to yield the corresponding fluorinated aromatic. Potassium fluoride is the most often used fluoride source. We tried therefore to perform $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-bromobenzaldehyde with imidazole with 1 mol of potassium fluoride. No positive effect of KF was observed, just starting material was detected in the reaction mixture (Entry 6).

One-step nucleophilic aromatic substitution reactions on 4-halobenzaldehydes which are less expensive than 4-fluorobenzaldehyde are very interesting from industrial point of view. We decided therefore to investigate if the application of microwave irradiation would not promote $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-halobenzaldehydes. We observed very positive effect of microwave irradiation in all $\text{S}_{\text{N}}\text{Ar}$ reactions studied in this work. Sonochemical $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-fluorobenzaldehyde with imidazole gave after 15 min sonication 75 % of 4-(imidazol-1-yl)benzaldehyde (*IIIa*) while the reaction performed under microwave irradiation gave after 15 min 95 % of the product *IIIa*. Effect of microwave irradiation was more expressive when less reactive 4-chlorobenzaldehyde and 4-bromobenzaldehyde were used as a starting material. Sonochemical reactions gave no product *IIIa* and starting material only was detected in the reaction mixtures. On the other hand, microwave irradiation-promoted $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-chlorobenzaldehyde gave after 5 min irradiation 39 % of *IIIa* and $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-bromobenzaldehyde gave at the same time 30 % of *IIIa*.

Having good results of reaction with imidazole, we decided to test the microwave effect on the $\text{S}_{\text{N}}\text{Ar}$ reaction with piperidine, which is, due to its higher ba-

slicity, more reactive both at thermal and sonochemical reactions with 4-fluorobenzaldehyde. Microwave-irradiated $\text{S}_{\text{N}}\text{Ar}$ reaction on the best reactive 4-fluorobenzaldehyde with piperidine gave after 5 min 63 % of 4-(piperidin-1-yl)benzaldehyde (*IIIb*). Sonochemical reaction gave after 15 min 85 % of *IIIb* and classical reaction gave after 5 h 48 % of *IIIb*. 4-Chlorobenzaldehyde as well as 4-bromobenzaldehyde were unreactive in the sonochemical $\text{S}_{\text{N}}\text{Ar}$ reactions with piperidine. Microwave-irradiated $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-chlorobenzaldehyde gave 3 % of *IIIb* and the $\text{S}_{\text{N}}\text{Ar}$ reaction on 4-bromobenzaldehyde gave 8 % of *IIIb*. Prolonging the reaction time of microwave-promoted reactions did not have any positive effect on the yields of $\text{S}_{\text{N}}\text{Ar}$ reactions. A lot of unidentified products were detected in the reaction mixtures. The low yields of $\text{S}_{\text{N}}\text{Ar}$ products with piperidine as the nucleophile at microwave experiments should be due to its low boiling point (106 °C). The high final temperature in the experiments 165–169 °C should cause the evaporation of piperidine from the reaction medium.

The solventless nucleophilic aromatic substitution with cyclic amines under microwave irradiation was described recently [4]. Basic alumina was used as energy-transfer medium. We decided therefore to check out if 4-halobenzaldehydes would not afford the $\text{S}_{\text{N}}\text{Ar}$ reactions at the same conditions. To our surprise, the experiments with 4-halobenzaldehydes *Ia—Ic* and amines *IIa, IIb* gave at the analogous conditions the products of the Cannizzaro reaction only (Scheme 2). The results obtained by us are therefore in contradiction with the results described in [4]. Later on we decided to modify the catalyst. Addition of 1 mol of potassium fluoride did not change the reac-



Scheme 3

tion course (Entry 4). Reactions with 1 mol of potassium carbonate without solvent as well as in ethanol without Al_2O_3 gave at the conditions described no product (Entries 5, 6) and just starting material was detected in the reaction mixture. These results are probably due to bad energy-transfer ability of potassium carbonate and low boiling point of ethanol. Basic alumina did not change the reaction course (Entry 9). To make sure that the reaction course was not due to the mechanochemical effect, we analyzed the reaction mixture directly after its grounding (30 min) in a mortar. Starting material only was detected in the reaction mixture. Exchange of imidazole by piperidine did not have any influence on the reaction course. The only products were products of the Cannizzaro reaction (Entry 11). Products of the Cannizzaro reaction were isolated at the reaction of 4-bromobenzaldehyde using neutral alumina even in the case when the reactions were performed without any amine (Entries 7, 8). This is a proof that imidazole and piperidine are just useless additives at the observed Cannizzaro reaction.

Another interesting reactions of aromatic aldehydes in the presence of inorganic solid were described recently [5]. Aromatic and heterocyclic aldehydes react with vinyl acetate to give aryl acetaldehyde enolates in THF in the presence of barium hydroxide. Yields of the products were 60–80 %, but the reaction time necessary to achieve such good results was 2–12 h. So, we decided to study these reactions under microwave and ultrasonic irradiation. Solventless reaction of 4-fluorobenzaldehyde gave after 3 min microwave irradiation 14 % of 4-fluorocinnamaldehyde (VIIa) (Scheme 3). The main products of this reaction were products of the Cannizzaro reaction. 24 % of 4-fluorobenzyl alcohol (IVa) was isolated from the reaction mixture. 4-Fluorobenzyl alcohol can react under these conditions with vinyl acetate to give 4-fluorobenzyl acetate (VIIIa) and 4 % of VIIIa was isolated by column chromatography (Table 3, Entry 1).

Results of the reaction of 4-chlorobenzaldehyde with vinyl acetate were similar. 4-Chlorobenzyl alcohol (IVb) was the main product of the Cannizzaro reaction. 77 % of it was isolated after the reaction. Just traces of 4-chlorocinnamaldehyde (VIIb) were detected in the reaction mixture by GC-MS as well as ^1H NMR spectroscopy (Entry 2). Prolonging the reaction time of the solventless reaction of 4-chlorobenzaldehyde with vinyl acetate in the presence of barium hydroxide octahydrate from 2 to 10 min increased the conversion to 96 %. 4-Chlorobenzyl alcohol (IVb) (37 % yield) was the main product and 21 % of 4-chlorobenzylacetate (VIIIb) was also isolated from the reaction mixture. Prolonging the reaction time did not affect the reaction course and just traces were detected again (Entry 3).

To check the role of water in barium hydroxide octahydrate we performed the reaction of 4-chlorobenzaldehyde with dried barium hydroxide. Conversion of starting material was 4 % instead of 90 % achieved using barium hydroxide octahydrate. The only product detected in the reaction mixture (4 %) was 4-chlorocinnamaldehyde (VIIb) (Entry 4).

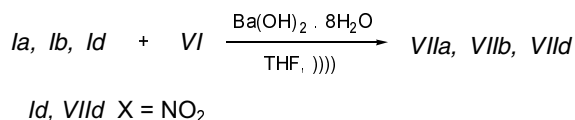
The same results were achieved when the reaction was performed in THF. Conversion of starting material was 4 % and the only product detected by GC-MS and ^1H NMR spectroscopy was 4-chlorocinnamaldehyde (VIIb) (Entry 5). This result is probably due to low boiling point of THF. The final temperature of the reaction mixture was 70 °C. We tried to perform this reaction in 2-chlorotoluene. The final temperature of the reaction mixture increased to 136 °C and the conversion of starting material increased from 5 % in the case of THF to 30 %. The main product of this reaction was again the Cannizzaro product. After the reaction 23 % of 4-chlorobenzyl alcohol (IVb) and 7 % of 4-chlorocinnamaldehyde (VIIb) were isolated (Entry 6).

Starting material only was detected in the reaction mixture after the reaction of 4-chlorobenzaldehyde

Table 4. Results of the Reactions of 4-X-Benzaldehydes *Ia, Ib, Id* with Vinyl Acetate *VI* under Ultrasonic Irradiation

Run	Base	X	Time	Yield/% of <i>VIIa, VIIb, VIII</i>
			min	
1	Ba(OH) ₂ · 8H ₂ O	F	30	10
2	Ba(OH) ₂ · 8H ₂ O	Cl	30	23
3	Ba(OH) ₂ · 0.7H ₂ O	Cl	30	0
4	Ba(OH) ₂ · 8H ₂ O	Cl	1440 (24 h)	< 1 ^a
5	Ba(OH) ₂ · 8H ₂ O	NO ₂	30	9

a) Yield of classical reaction, thermal heating, stirring, temperature of boiling THF.



Scheme 4

with vinyl acetate in the presence of potassium carbonate instead of barium hydroxide (Entry 7).

As the described process [5] is a heterogeneous reaction we decided to test if ultrasound would not enhance the reaction rate. We found out that there is no Cannizzaro reaction going on and the only products of the reactions of 4-halobenzaldehydes with vinyl acetate in THF under ultrasonic irradiation were 4-halocinnamaldehydes. Reaction of 4-fluorobenzaldehyde with vinyl acetate in the presence of barium hydroxide octahydrate gave after 30 min sonication 10 % of 4-fluorocinnamaldehyde (*VIIa*) (Scheme 4, Table 4, Entry 1). The analogous reaction with 4-chlorobenzaldehyde gave 23 % of 4-chlorocinnamaldehyde (*VIIb*) (Entry 2). Using dried barium hydroxide (C-200 catalyst) instead of barium hydroxide octahydrate did not afford any reaction. Starting material only was detected in the reaction mixture. Reaction of 4-nitrobenzaldehyde with vinyl acetate in the presence of barium hydroxide

octahydrate gave after 30 min sonication 9 % of 4-nitrocinnamaldehyde (*VIII*) (Entry 5). The low yields of substituted cinnamaldehydes at sonochemical reactions prompted us to check the described silent procedure [5]. To our surprise, thermal reaction of 4-chlorobenzaldehyde with vinyl acetate gave just traces of 4-chlorocinnamaldehyde (*VIIb*) (Entry 4) after 24 h of reaction. This result is throwing some doubts on the results described in [5].

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