ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2010, *55*(11-12), 983-987

Dedicated to the memory of
Professor Ioan Silaghi-Dumitrescu (1950 – 2009)

ULTRASOUNDS-ASSISTED SYNTHESIS OF HIGHLY FUNCTIONALIZED ACETOPHENONE DERIVATIVES IN HETEROGENEOUS CATALYSIS

Gheorghiță N. ZBANCIOC,[a] Ana Maria V. ZBANCIOC,[b] Dorina MANTU,[a] Anca MIRON,[b] Cătălin TĂNASE[c] and Ionel I. MANGALAGIU[a*]

[a] "Al. I. Cuza" University of Iasi, Faculty of Chemistry, Organic Chemistry Department, Bd. Carol 11, 700506 Iasi, Roumania
[b] "Gr.T.Popa" University, Faculty of Farmacy of Iasi, Str. Universitatii 16, 700115 Iasi, Roumania
[c] "Al. I. Cuza" University of Iasi, Faculty of Biochemistry, Bd. Carol 11, 700506 Iasi, Roumania

Received March 18, 2010

A fast, general, environmentally friendly, and facile method for preparation of highly functionalized acetophenone derivatives under ultrasound irradiation in heterogeneous catalysis is presented. The ultrasound enhanced a remarkable rate of acceleration for bromination, the reaction time decrease significantly, reaction conditions are milder, the consumed energy decreases considerably and the amount of used solvents was reduced. Consequently, the ultrasounds-assisted bromination reaction could be considered eco-friendly. In the most cases under ultrasound irradiation the yields are higher, in some cases substantially. A comparative study, ultrasounds-conventional conditions was done.

INTRODUCTION

Recently published comprehensive books[1] and papers[2] indicate chemical applications of ultrasounds. "Sonochemistry" is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of synthesis. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in higher yields, shorter reaction time and milder conditions.[1,2] Furthermore, reactions under ultrasound have the great advantage of using small amounts of organic solvents, thus such reactions are more environmentally friendly and generate less side products.

Synthesis of highly functionalized acetophenone derivatives is an important goal for organic synthesis, these derivatives being key intermediates in obtaining of fused heterocyclic, of both theoretical and practical interest such as biologically active compounds[3-6] (antiviral, anticancer, antituberculosis, antihypertensive, antimicrobial, etc.), optoelectronic materials[7](for sensors and biosensors, electroluminescent materials, lasers), etc. One of the strategy adopted to obtain highly functionalized acetophenone involve α-bromination of acetophenone derivatives, either with molecular bromine either in heterogeneous catalysis.[8] The last method have some advantages in terms of yields and selectivity being more and more used. Moreover, the bromination in heterogeneous catalysis is included in the eco-friendly domain, because using of copper(II) bromide offers a viable alternative to molecular bromine which is highly toxic and difficult to handle.

In continuing of our work within this area,[5,9] we report herein an efficient, general and eco-friendly

* Corresponding author: ionelm@uaic.ro

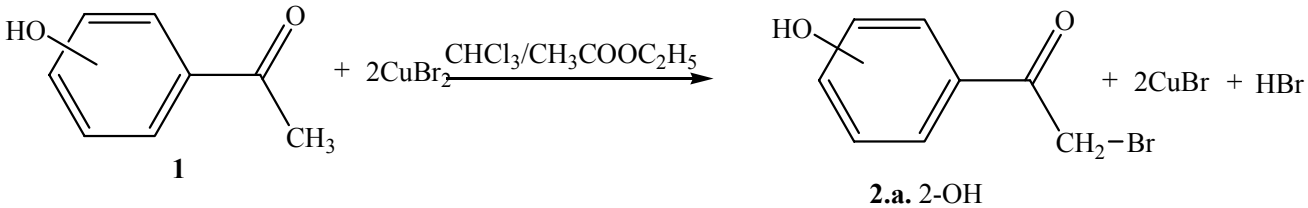
method for preparation of highly functionalized acetophenone derivatives using ultrasound irradiation in heterogeneous catalysis.

RESULTS AND DISCUSSION

In order to obtain highly functionalized acetophenone derivatives, we perform the bromination reaction of variously acetophenones with copper(II) bromide, both under conventional heating and ultrasounds irradiation (Schemes 1-3).

The bromination of hydroxyacetophenones (2-; 3- and 4-) lead to ω-bromo-hydroxyacetophenones **2**, and occur highly selective (no nuclear bromination was observed), in good yields (Scheme 1, Table 1).

Unexpectedly, the bromination of dihydroxyacetophenone (2,4-; 2,5-, 2,6-, 3,4- and 3,5-) did not occur according with our expectations, having some particular aspects (Scheme 2, Table 2).

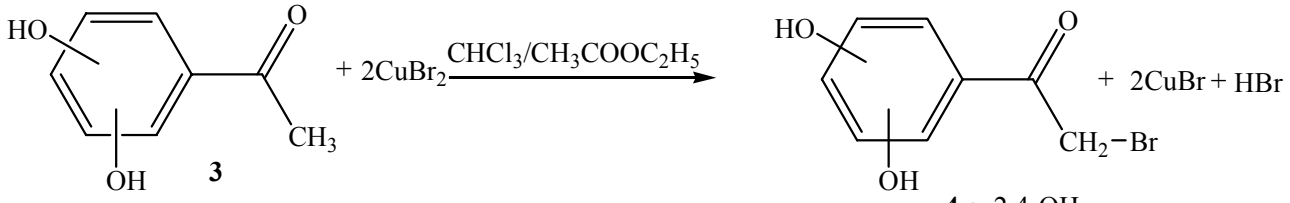


1

2-OH; 3-OH; 4-OH

2.a. 2-OH
b. 3-OH
c. 4-OH

Scheme 1 – Reaction pathways to obtain ω-bromo-hydroxyacetophenone **2a-c.**

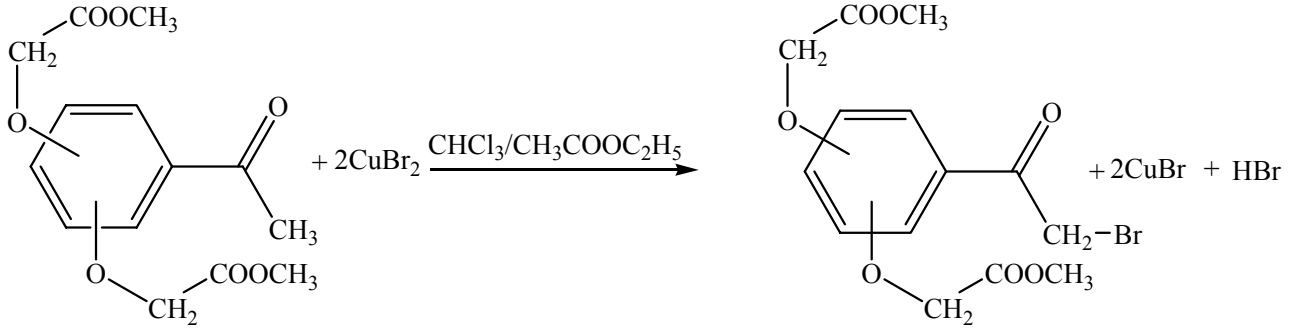


3

2,4-OH; 2,5-OH; 2,6-OH
3,4-OH; 3,5-OH

4.a. 2,4-OH
b. 2,5-OH
c. 2,6-OH
d. 3,4-OH
e. 3,5-OH

Scheme 2 – Reaction pathways to obtain ω-bromo-dihydroxyacetophenones **4a-e.**



5

2,4-OR; 2,5-OR; 2,6-OR
3,4-OR; 3,5-OR

6.a. 2,4-OR
b. 2,5-OR
c. 2,6-OR
d. 3,4-OR
e. 3,5-OR

Scheme 3 – Reaction pathways to obtain dietherificated acetophenones **6a-e.**

No matter the condition we employed, we obtained only traces of desired ω-bromo-dihydroxyacetophenones **4**, and starting materials left. Incomplete reaction is indicated by finding unreacted copper(II) bromide in the final reaction mixture and by total ion chromatograms (TIC) for a sample with 2',4'-dihydroxyacetophenone (Figure 1). Having in view the above consideration, we decide to etherificate first the dihydroxyacetophenones (blocking the OH groups) and than to perform the bromuration. In this case the bromination reaction was successfull, ω-bromo-di-OR-acetophenones **6** being obtained in good yields and higly selective (no nuclear bromination was observed), Scheme 3.

As indicated in Table 1, ultrasound irradiation induces a remarkable acceleration for reactions, the reaction times decreasing dramatically, from hours to minutes. Consequently, the consumed energy decrease considerably, these reactions being considered eco-friendly. We could also notice that, under ultrasound irradiation the yields are higher by a average of 10–15%. We presume that the efficiency of using ultrasound irradiation is due to the cavitations phenomena, the energy being more efficiently transmitted to the substrates compared to the reactions performed at room temperature. Also, the collapse of bubbles induces mechanical stress that can be transmitted to a target single bond, this phenomena being a specificity of ultrasound action.

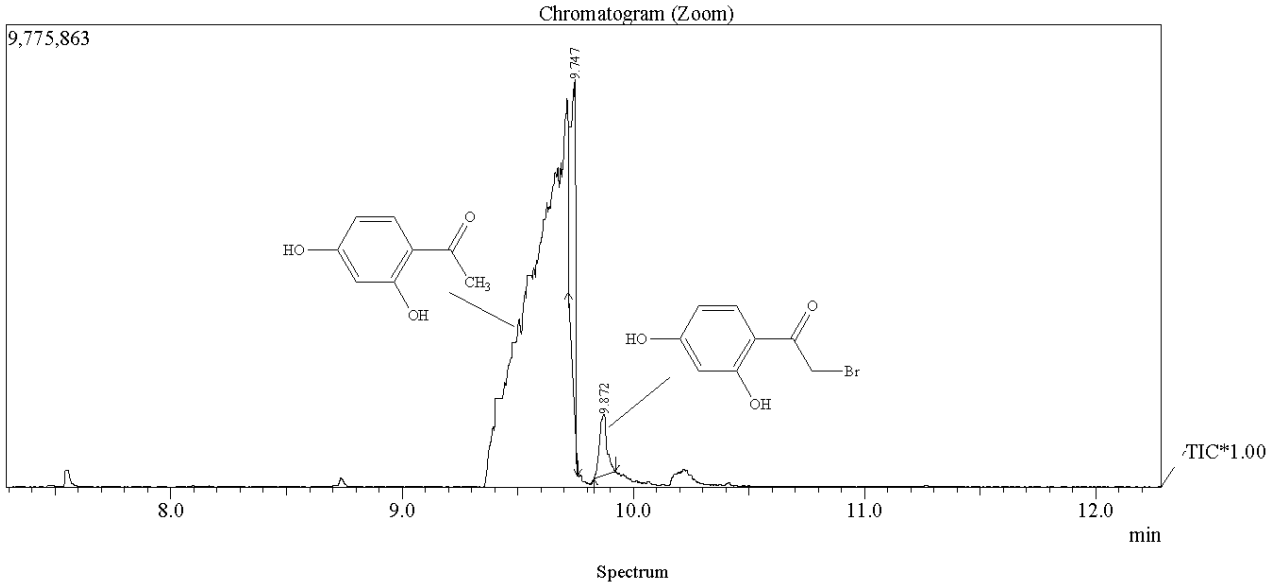


Fig. 1 – Total ion chromatograms for the bromination of 2,4-dihydroxyacetophenone.

Table 1

Syntheses of highly functionalized acetophenones under ultrasounds and conventional bromuration, in heterogeneous catalysis

Compound	Ultrasounds		Conventional	
	Reaction time, min.	Yield, %	Reaction time, min.	Yield, %
2.a	20	64	180	63
2.b	20	80	180	67
2.c	20	85	180	74
4.a	20	2	300	3
4.b	20	5	300	6
4.c	20	5	300	5
4.d	20	78	300	63
4.e	20	77	300	65
6.a	20	86	300	71
6.b	20	88	300	75
6.c	20	84	300	69
6.d	20	83	300	76
6.e	20	80	300	65

The structure of compounds was proven by elemental (C, H, N) and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). All the elemental and spectral data are in accordance with the proposed structure and are presented in the experimental part.

EXPERIMENTAL

Apparatus and analysis

All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra ($CDCl_3$), and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) were recorded on a Bruker Avance 400 DRX spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts are given in ppm (δ-scale,), coupling constants (*J*) in Hz. The IR spectra were recorded in KBr on a FT-IR Shimadzu Prestige 8400s spectrophotometer. Ultrasound assisted reactions were carried out using a Sonics reactor (Bandelin, Sonoplus GM 3200, Germany) with a frequency of 20 KHz and a nominal power of 200 W.

The GCMS-QP 2010 operated in chemical ionization (CI) mode. The system was eguipped with a 25 m x 0.25 mm x 0.25 μm DB-5ms capillary column. The ion source, quadrupole and interface temperatures were 330 ^{o}C. Helium was used as carrier gas at constant flow (1.54 mL/min) with an initial pressure of 90.7 kPa, while methane was used as reagent gas in the mass spectrometer. The electron multiplier voltage was set at 1250 V. Two microliters of diluted solution was injected in cold pulsed splitless mode (initial injector temperature at 250 ^{o}C). The temperature of the AT-5 column was programated from 50 ^{o}C, stay 2 min, then to 320 ^{o}C at a rate of 15 ^{o}C/min, stay 5 min then to 320 ^{o}C.

General procedure for syntheses of ω-bromo-acetophenones under conventional heating

To a suspension of 25 mmol (5,58 g) of copper(II) bromide in 20 mL chloroform, 12.5 mmol of acetophenone (1.70 g of hydroxyacetophenone or 1.90 g of dihydroxyacetophenone) is added dropwise in one hour under stirring and refluxing. The stirring and reflux were continued for a period of 180 to 300 min. The copper(I) bromide was filtred off and the solvent was removed by distillation under reduced pressure. The product was crystallized from toluene.

General procedure for syntheses of ω-bromo-acetophenones under ultrasound irradiation

Ultrasound assisted reactions were carried out using the Sonoplus GM 3200 reactor, and, the best results were obtained when a pulse irradiation was applied: 5 s pulse/ 5 s pause, 65% from the full power of the generator.

A solution of 25 mmol (5,58 g) of copper(II) bromide in a mixture of 30 mL chloroform/ethylacetate in ratio 1:2 and 12.5 mmol of acetophenone (1.70 g of hydroxyacetophenone or 1.90 g of dihydroxyacetophenone), was exposed to ultrasound for 20 min. The resulting mixture was filtered off and the solvent was removed by distillation under reduced pressure. The final product was crystallized from toluene.

2-bromo-1-(2-hydroxyphenyl)ethanone (2.a). Obtained from 1-(2-hydroxyphenyl)ethanone, as yellow oil. Calc. for $C_8H_7BrO_2$ (215): C 44.68, H 3.28; found: C 44.60, H 3.21. **IR** (KBr, cm-1): 3329 (OH), 3075 (C-H arom.), 2958 (C-H aliph.), 1681 (C=O ceto), 1600, 1568, 1511 (C=C), 1268, 1177 (C-O), 687 (C-Br). **^{1}H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 4.89 (s, 2H: H_2), 6.96 (dt, *J*= 7.2, *J*= 8.0, 1H: $H_{5'}$), 7.01 (dd, *J*= 8.4, *J*= 0.8, 1H: $H_{3'}$), 7.52 (dt, *J*= 8.4, *J*= 7.2, 1H: $H_{4'}$), 7.82 (dd, *J*= 8.0, *J*= 1.6, 1H: $H_{6'}$), 11.22 (s, 1H: OH). **^{13}C-NMR** (TMS, $CDCl_3$, δ, ppm): 36.12 (C_2), 117.54 ($C_{3'}$), 119.30 ($C_{5'}$), 119.91 ($C_{1'}$), 130.86 ($C_{6'}$), 135.93 ($C_{4'}$), 159.53 ($C_{2'}$), 194.55 (C_1: C=O). **MS (CI, m/z):** 217 (14%), 215 (14%), 121 (100%), 107 (8%).

2-bromo-1-(4-hydroxyphenyl)ethanone (2.c). Obtained from 1-(4-hydroxyphenyl)ethanone, as brown crystals. Calc. for $C_8H_7BrO_2$ (215): C 44.68, H 3.28; found: C 44.62, H 3.23. **IR** (KBr, cm-1): 3332 (OH), 3090 (C-H arom.), 2989 (C-H aliph.), 1676 (C=O ceto), 1602, 1573, 1514 (C=C), 1282, 1197 (C-O), 692 (C-Br). **^{1}H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 4.78 (s, 2H: H_2), 6.89 (d, *J*= 8.8, 2H: $H_{3'}$, $H_{5'}$), 7.89 (d, *J*= 8.8, 2H: $H_{2'}$, $H_{6'}$), 10.55 (s, 1H: OH). **^{13}C-NMR** (TMS, $CDCl_3$, δ, ppm): 33.95 (C_2), 115.91 ($C_{3'}$), 125.87 ($C_{1'}$), 131.95 ($C_{2'}$), 163.16 ($C_{4'}$), 190.37 (C_1: C=O). **MS (CI, m/z):** 217 (27%), 215 (24%), 137 (100%), 121 (46%), 107 (8%).

2-bromo-1-(2,4-dihydroxyphenyl)ethanone (4.a). Obtained from 1-(2,4-dihydroxyphenyl)ethanone, as white-yellow crystals. Calc. for $C_8H_7BrO_3$ (230): C 41.59, H 3.05; found: C 41.62, H 3.02. **IR** (KBr, cm-1): 3377 (OH), 3076 (C-H arom.), 2943 (C-H aliph.), 1672, (C=O ceto), 1599, 1475, 1412 (C=C), 1299, 1167, 1123 (C-O), 634 (C-Br). **^{1}H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 4.81 (s, 2H: H_2), 6.65 (s, 1H: $H_{3'}$), 6.79 (d, *J*= 9.2, 1H: $H_{5'}$), 8.17 (d, *J*= 9.2, 1H: $H_{6'}$), 12.61 (s, 1H: OH-4) , 13.50 (s, 1H: OH-2). **^{13}C-NMR** (TMS, $CDCl_3$, δ, ppm): 33.76 (C_2), 102.68 ($C_{3'}$), 108.72 ($C_{5'}$), 113.26 ($C_{1'}$), 135.51 ($C_{6'}$), 164.11 ($C_{4'}$), 164.78 ($C_{2'}$), 196.51 (C_1: C=O). **MS (CI, m/z):** 232 (32%), 230 (31%), 217 (100%), 215 (98%), 137 (13%), 108 (16%).

2-bromo-1-(3,5-dihydroxyphenyl)ethanone (4.e). Obtained from 1-(3,5-dihydroxyphenyl)ethanone, as white-grey crystals. Calc. for $C_8H_7BrO_3$ (230): C 41.59, H 3.05; found: C 41.59, H 3.01. **IR** (KBr, cm-1): 3388 (OH), 3064 (C-H arom.), 2993 (C-H aliph.), 1685, (C=O ceto), 1595, 1465, 1389 (C=C), 1340, 1170, 1157 (C-O), 675 (C-Br). **^{1}H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 4.79 (s, 2H: H_2), 6.50 (s, 1H: $H_{4'}$), 6.82 (d, 2H: $H_{2'}$, $H_{6'}$), 9.69 (s, 1H: OH). **^{13}C-NMR** (TMS, $CDCl_3$, δ, ppm): 34.21 (C_2), 106.65 ($C_{2'}$, $C_{6'}$), 107.80 ($C_{4'}$), 135.81 ($C_{1'}$), 158.65 ($C_{3'}$, $C_{5'}$), 191.45 (C_1: C=O). **MS (CI, m/z):** 232 (15%), 230 (15%), 137 (100%), 123 (15%), 109 (24%).

dimethyl 2,2'-(4-(2-bromoacetyl)-1,3-phenylene)bis(oxy) diacetate (6.a). Obtained from dimethyl 2,2'-(4-acetyl-1,3-phenylene)bis(oxy)diacetate, as white-grey crystals. Calc. for $C_{14}H_{15}BrO_7$ (375): C 44.82, H 4.03; found: C 44.76, H 3.97. **IR** (KBr, cm-1): 3082 (C-H arom.), 2954, 2944 (C-H aliph.), 1748, (C=O est.), 1701 (C=O ceto), 1598, 1472, 1437 (C=C), 1235, 1188, 1097 (C-O), 657 (C-Br). **^{1}H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 3.80 (s, 3H: CH_3; COOMe from 4' position), 3.82 (s, 3H: CH_3; COOMe from 2' position), 4.63 (s, 2H:

CH_2–O from 4' position), 4.73 (s, 2H: CH_2–O from 2' position), 4.77 (s, 2H: CH_2–Br), 6.83 (d, *J*= 8.0, 1H: $H_{5'}$), 7.12 (d, *J*= 8.0, 1H: $H_{6'}$), 7.35 (s, 1H: $H_{3'}$). **^{13}C-NMR** (TMS, $CDCl_3$, δ, ppm): 37.64 (CH_2–Br), 52.27 (CH_3:COOMe from 4' position), 52.44 (CH_3:COOMe from 2' position), 65.71 (CH_2–O from 4' position), 66.11 (CH_2–O from 2' position), 114.14 ($C_{5'}$), 115.81 ($C_{6'}$), 122.30 ($C_{3'}$), 125.83 ($C_{1'}$), 151.77 ($C_{4'}$), 152.59 ($C_{2'}$), 168.35 (C=O_{est} from 4' position), 168.97 (C=O_{est} from 2' position), 191.60 (C_1: C=O_{ceto}). **MS (CI, m/z):** 376 (55%), 374 (53%), 317 (70%), 315 (74%), 281 (62%), 253 (100%).

dimethyl 2,2'-(5-(2-bromoacetyl)-1,3-phenylene)bis(oxy) diacetate (6.e). Obtained from dimethyl 2,2'-(5-acetyl-1,3-phenylene)bis(oxy)diacetate, as white-grey crystals. Calc. for $C_{14}H_{15}BrO_7$ (375): C 44.82, H 4.03; found: C 44.84, H 3.99. **IR** (KBr, cm-1): 3089 (C-H arom.), 2979, 2948 (C-H aliph.), 1749, (C=O est.), 1704 (C=O ceto), 1595, 1458, 1436 (C=C), 1220, 1166, 1093 (C-O), 653 (C-Br). **^{1}H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 3.71 (s, 6H: 2xCH_3), 4.89 (s, 4H: 2xCH_2–O), 4.92 (s, 2H: CH_2–Br), 6.86 (s, 1H: $H_{4'}$), 7.15 (s, 2H: $H_{2'}$, $H_{6'}$). **^{13}C-NMR** (TMS, $CDCl_3$, δ, ppm): 34.20 (CH_2–Br), 51.81 (2xCH_3), 64.79 (2xCH_2–O),106.66 ($C_{4'}$), 107.69 ($C_{2'}$, $C_{6'}$), 135.88 ($C_{1'}$), 158.83 ($C_{3'}$, $C_{5'}$), 168.90 (2x C=O_{est}), 191.14 (C_1: C=O_{ceto}). **MS (CI, m/z):** 376 (23%), 374 (21%), 317 (9%), 315 (9%), 296 (66%),297 (17%), 281 (100%).

CONCLUSIONS

In conclusion, a new, fast, general, and facile method for preparation of highly functionalized acetophenone derivatives under ultrasound irradiation is presented. Ultrasounds induce a remarkable acceleration for reactions, the reaction times decreasing dramatically from hours to minutes, the consumed energy decrease considerably, the reaction conditions are milder, the yields are higher and the amount of used solvents is reduced. Consequently, the ultrasound assisted bromination reaction could be considered eco-friendly. A comparative study, ultrasounds-conventional conditions was done.

Acknowledgements: This work was financially supported by the Roumanian Ministry of Education and Research, grant C.N.C.S.I.S. cod 88 under PN-II-ID-PCE-2008 Program.

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