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Ultrasonic Irradiation Assisted Enantioselective Synthesis of Alzheimer's Disease Drug Rivastigmine Tartrate by Using Nanocatalyst

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Abstract

A highly efficient and convenient procedure for the enantioselective synthesis of (*S*)-Rivastigmine tartrate, a cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's disease, is accomplished by the treatment of versatile, readily accessible *N*-Ethyl-*N*-methyl carbamoyl chloride with 3-hydroxyacetophenone under ultrasonic irradiation in presence of nano-K_2CO_3were reported. This protocol provided a high yielding stereoselective and short synthesis of (*S*)-Rivastigmine tartrate with an overall isolated yield of 83%. All the starting reagents and catalyst are inexpensive and commercially available.Compared to conventional heating which provides thermal energy in the macro system, ultra sonification reduces reaction times, improves yields and minimizes side product formation by providing the activation energy in micro environment. As this technology involves energy conservation and minimal waste generation, it is widely accepted as a green chemistry approach. The reported strategy afforded under ultrasonic irradiation and in presence of Nano-K_2CO_3 via four steps, which (to the best of our knowledge) depicts the shortest and the most rapid method to enantiopure Rivastigmine tartrate reported to date.

Keywords:*Synthesis, Rivastigmine,Nano-K_2CO_3,Alzheimer's disease,Ultrasonic irradiation.*

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Introduction

Alzheimer's disease (AD) is the most common form of dementia, a severe human health threat with more than 30 million sufferers worldwide [1]. Rivastigmine, (*S*)-3- [1-(dimethylamino)ethyl] phenyl ethyl (methyl) carbamate (Figure 1), is the first USFDA approved drug in the form of capsules and patches for the treatment of mild to moderate dementia of the Alzheimer's type [2-5] and for mild to moderate dementia related to Parkinson's disease [6]. (S)-Rivastigmine acts as potent cholinesterase inhibitor and represents one of the most potent agents for the treatment of Alzheimer's and Parkison's disease at early stages [7,8]. However, only the (S)-enantiomer exhibits the desired biological activity [8], which intrinsically requires the drug to be administered in enantiomerically pure form. To date, several asymmetric methods have been developed for the preparation of enantiopure Rivastigmine such as racemate resolution using chiral acids [9], asymmetric addition of organozinc species onto imines using transition metal catalysis [10], diastereoselective reductive amination [11], lipase-catalyzed (dynamic) kinetic resolution of a hydroxy-precursor [12], and recently an asymmetric total synthesis of Rivastigmine by forming the chiral amine moiety via enzymatic amination of the corresponding ketone employing u-transaminases (u-TAs) were reported [13]. In recent years, ultrasound irradiation has gained recognition as a clean and advantageous approach in organic synthesis. The sonochemical phenomenon is the result of the interaction of suitable field of acoustic waves with potentially reacting chemical system. This phenomenon occurs through acoustic cavitation. The phenomenon of cavitation in an irradiated solution may be expressed as a sequential process of involving the bubble formation, its growth and breakdown. Cavitation phenomenon develops high temperature and pressure in the micro environment which creates turbulence and facilitates the mass transfer in the neighborhood. Compared to conventional heating which provides thermal energy in the macro system, ultra sonification reduces reaction times, improves yields and minimizes side product formation by providing the activation energy in micro environment. As this technology involves energy conservation and minimal waste generation, it is widely accepted as a green chemistry approach. Furthermore, this technique can be applied to a variety of organic syntheses accomplishing better yields, under mild reaction conditions and shorter reaction times (Table 1).However, there are various drawbacks for these methods such as complex operations, loss of yield, metal impurities in final API, multiple purification procedures in the lipase catalyzed resolution, three enzyme systems in the transaminase reactions, and the need for multiple crystallization steps with chiral acids [10-13].Herein we wish to report a practical, high yield and excellent enantiomeric excess in a four steps synthesis of (S)-Rivastigmine in presence of Nano-K_2CO_3.

Table 1. Comparison of rivastigmine tartrate synthesis methods.

No.	Reference No.	Yield (%)	Total reaction Time	Catalysts and Reagent availability
1	10	50	Several days	Expensive catalysts
2	11	70	Several days	Expensive catalysts
3	12	40	Several days	Expensive catalysts
4	13	58	Several days	Expensive catalysts
5	This study	83	Less than a day	Inexpensive catalysts and reagents

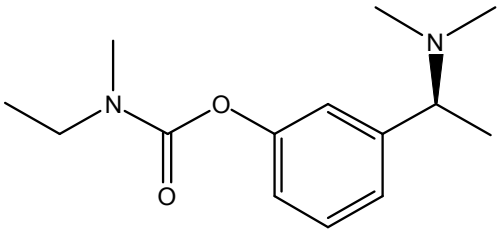

Figure 1. Structure of (S)-Rivastigmine

Experimental

General

Anhydrous EtOH was freshly distilled from calcium hydride. All solvents and reagents are reagent grade pure and used without further purification. All melting points are determined on Polmon MP-96 melting point apparatus. ^{1}H &^{13}C NMR spectra are recorded using a Bruker 400 MHz spectrometer (400 & 100 MHz respectively) with TMS as internal standard. Mass spectra are recorded on a Perkin-Elmer mass spectrometer operating at an ionization potential of 70 eV. IR spectra are recorded on Perkin Elmer spectrophotometer as KBr pellets or neat. Analytical TLC is conducted on E-Merck 60F254 aluminum-packed silicagel plates (0.2 mm). Developed plates are visualized under UV light or Iodine chamber. Chiral HPLC spectra are recorded on Waters alliance 2695 with 2487 U. V. detector.

Synthesis and regeneration of Nano-K_2CO_3

Anhydrous K_2CO_3 (150 g), absolute ethanol (63 mL), and lauric acid (0.435 g) were poured into a resonance mill. The mixture was milled at room temperature for 8 h. After reaction completion, the mixture was filtered and washed with ethanol (3 × 30 mL). The filter cake was calcined in muffle at 250 °C for 4 hours to generate normal K_2CO_3 with ≥95% yield. The normal K_2CO_3 was milled again as the procedure of preparation of nano-K_2CO_3. Nano-K_2CO_3 was obtained and the average particle size of the particles was still 64 nm measured by laser particle size analyzer [17].

*Synthesis of 3-Acetylphenyl Ethyl (methyl) carbamate (**3**)*

3.4 g (25 mmol) m-hydroxyacetophenone (1), 4.8 g (34.7 mmol) Nano-K_2CO_3 and 30 mL ethyl acetate were added to 3.3 g (27.1 mmol) N-ethyl-N-methyl carbamoyl chloride (2). The resulting suspension was then placed under ulterasonic and reflux, and the batch was agitated at this temperature for 1 h. After the batch cooled to room temperature, water (15 mL) was added, and the batch was agitated for a further 20 min. The phases were separated, and the aqueous layer was extracted with ethyl acetate (6 mL × 2). The organic phase was combined and then dried over anhydrous Na_2SO_4, filtered and evaporated to get 3-acetylphenyl ethyl (methyl) carbamate (3) (5.52 g, 99% yield) as a pale-yellow oil. IR (Neat, *ν*max, cm^{-1}): 1724 (C = O), 1686 (C = O), 2974 (aliphatic CH); 1H-NMR (400MHz, $CDCl_3$): δH 7.74 (*d*, 1H, *J* = 7.6 Hz, ArH), 7.65 (*s*, 1H, ArH), 7.40 (*t*, 1H, *J* = 7.9 Hz, ArH), 7.30 (*d*, 1H, *J* = 7.5 Hz, ArH), 3.42 (*q*, 1H, *J* = 7.0 Hz, rotamer1 CH_2), 3.37 (*q*, 1H, *J* = 7.0 Hz, rotamer2 CH_2), 3.04 (*s*, 1.5H, rotamer1 CH_3), 2.95 (*s*, 1.5H, rotamer2 CH_3), 2.55 (*s*, 3H, CH_3), 1.21 (*t*, 1.5H, *J* = 7.0 Hz, rotamer1 CH_3), 1.15 (*t*, 1.5H, *J* = 7.0 Hz, rotamer2 CH_3); 13C NMR (100MHz, $CDCl_3$): δC 197.08 (1C, C=O), 153.99 (*d*, *J* = 15.0 Hz, 1C, C=O), 151.64 (C_{aryl}), 138.19 (C_{aryl}), 129.26 (C_{aryl}), 126.57 (C_{aryl}), 124.93 (C_{aryl}), 121.47 (C_{aryl}), 43.98 (1C, CH_2 of carbamoyl), 34.14 (rotamer1 Mecarbamoyl), 33.70 (rotamer2 Mecarbamoyl), 26.56 (1C, CH_3), 13.10 (rotamer1 Mecarbamoyl), 12.29 (rotamer2 Mecarbamoyl); ESI-MS *m/z* (%): 222.0 (M^+, 100), 223.1 (M^+ + H, 20).

*Synthesis of 3-(1-Hydroxyethyl)phenyl ethyl(methyl)carbamate (**4**)*

To a solution of 3-Acetylphenyl Ethyl (methyl) carbamate (3) (2 g, 9.04 mmol) in dry methanol (7mL) sodiumborohydride (342mg, 9.04 mmol) was added at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 10 min. After completion of the reaction was confirmed by TLC, the reaction was quenched by careful addition of H_2O (2 mL), and methanol was evaporated. The residue was extracted with CH_2Cl_2/H_2O, and the organic layers were combined and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide 10 as a colorless oil (2 g, 99% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, J = 7.6 Hz, 1H), 7.11−7.07 (m, 2H), 6.95 (d, J = 7.6 Hz, 1H), 4.71 (q, J = 6.4 Hz, 1H), 3.68 (br s, 1H), 3.39 (dq, J = 6.8, 33.6 Hz, 2H), 2.97 (d, J= 41.6 Hz, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.18 (dt, J = 6.8, 25.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6 (d), 151.4, 147.9 (d), 129.0, 122.3, 120.3, 118.8, 69.4, 44.0, 34.2, 33.8, 25.0, 13.2, 12.4; HRMS (ESI) calcd for [M^+ K, $C_{12}H_{17}KNO_3$]+: 262.0846, Found 262.0848.

*Synthesis of 3-(1-(Dimethylamino)ethyl)phenyl ethyl(methyl)-carbamate (**5**)*

To a solution of 3-(1-Hydroxyethyl) phenyl ethyl(methyl)carbamate (4) (1 g, 4.5 mmol) in dry CH_2Cl_2 (16 mL) was added distilled triethylamine (2 mL, 13.5 mmol) at 0 °C under argon atmosphere and the reaction solution was stirred for 10 min. Methanesulfonyl chloride dissolved in dry CH_2Cl_2 (v/v10%, 5 mL, 5.9 mmol) was added to the cold reaction mixture dropwise over 30 min at 0 °C. The reaction solution was stirred at 0 °C for 1 h, dimethylamine (2M solution in THF, 10 mL) was added, and the reaction mixture was stirred at room temperature under ultrasonic irradiation for 2 h. After completion of the reaction was confirmed by TLC, the reaction mixture was poured in 1M HCl and extracted with CH_2Cl_2 and the organic layer was extracted again with 1M HCl. Both aqueous layers were combined and neutralized with 2 M NaOH until the pH was above 10 and then extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure to provide oily 3-(1-(Dimethylamino)ethyl)phenyl ethyl(methyl)-carbamate (1.2 g, 89% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.0 Hz, 1H), 7.12−7.00 (m, 3H), 3.43 (dq, J = 7.2, 24.0 Hz, 2H), 3.24 (q, J = 6.8 Hz, 1H), 3.02 (d, J = 29.6 Hz, 3H), 2.20 (s, 6H), 1.36 (d, J= 6.8 Hz, 3H), 1.21 (dt, J = 7.2, 20.8 Hz, 3H); 13C NMR (100 MHz, $CDCl_3$): δ 154.8 (d), 151.8, 146.0, 129.1, 124.5, 121.0, 120.5, 65.9, 44.3, 43.4, 34.4, 34.0, 20.3, 13.5, 12.7; HRMS (ESI) calcd for $[M + H, C_{14}H_{23}N_2O_2]^+$: 251.1760, Found 251.1765.

*Synthesis of S-Rivastigmine Tartrate (**6**)*

2.83 g L-(+)-Tartaric acid (18.9 mmol) was added to 4.72 g 3-(1-(Dimethylamino)ethyl)phenyl ethyl(methyl)-carbamate (18.9 mmol) in 30 ml acetone. The mixture was heated to reflux for 1 h and left to cool to room temperature. It crystallized at 0°C for 12 h. The precipitated white crystalline product was sucked off, washed with cold acetone, and vacuum dried. Finally, 6.9 g (94.8% yield, 99.8% HPLC purity) of the desired product were obtained. Mp 123–124 °C (lit. 123–125 °C), IR (KBr), cm^{-1}: 3319.2, 2977.9, 2934.2, 2874.8, 1714.5, 1595.9; ^{1}H NMR ($CDCl_3$) d: 1.17, 1.23 (2t, 3H), 1.68 (d, 3H), 2.65 (s, 6H), 2.96, 3.06 (2s, 3H), 3.38, 3.46 (2q, 2H), 4.36 (q, 1H), 4.47 (s, 2H), 7.14 (t, 1H),7.21 (s, 1H), 7.28 (t, 1H), 7.39 (t, 1H), 8.42 (br, 4H); ^{13}C NMR ($CDCl_3$) d 176.2, 154.3, 154.1, 151.8, 135.1, 130.0, 126.1, 123.1, 122.7, 72.5, 65.0, 44.2, 40.3, 34.2, 33.9, 16.5, 13.2, 12.4; MS (ESI) m=z: 251.08 (M+1). Anal. calcd. for $C_{18}H_{28}N_2O_8$: C, 53.99; H, 7.05; N, 7.0. Found: C, 53.91; H, 7.08; N, 6.93.

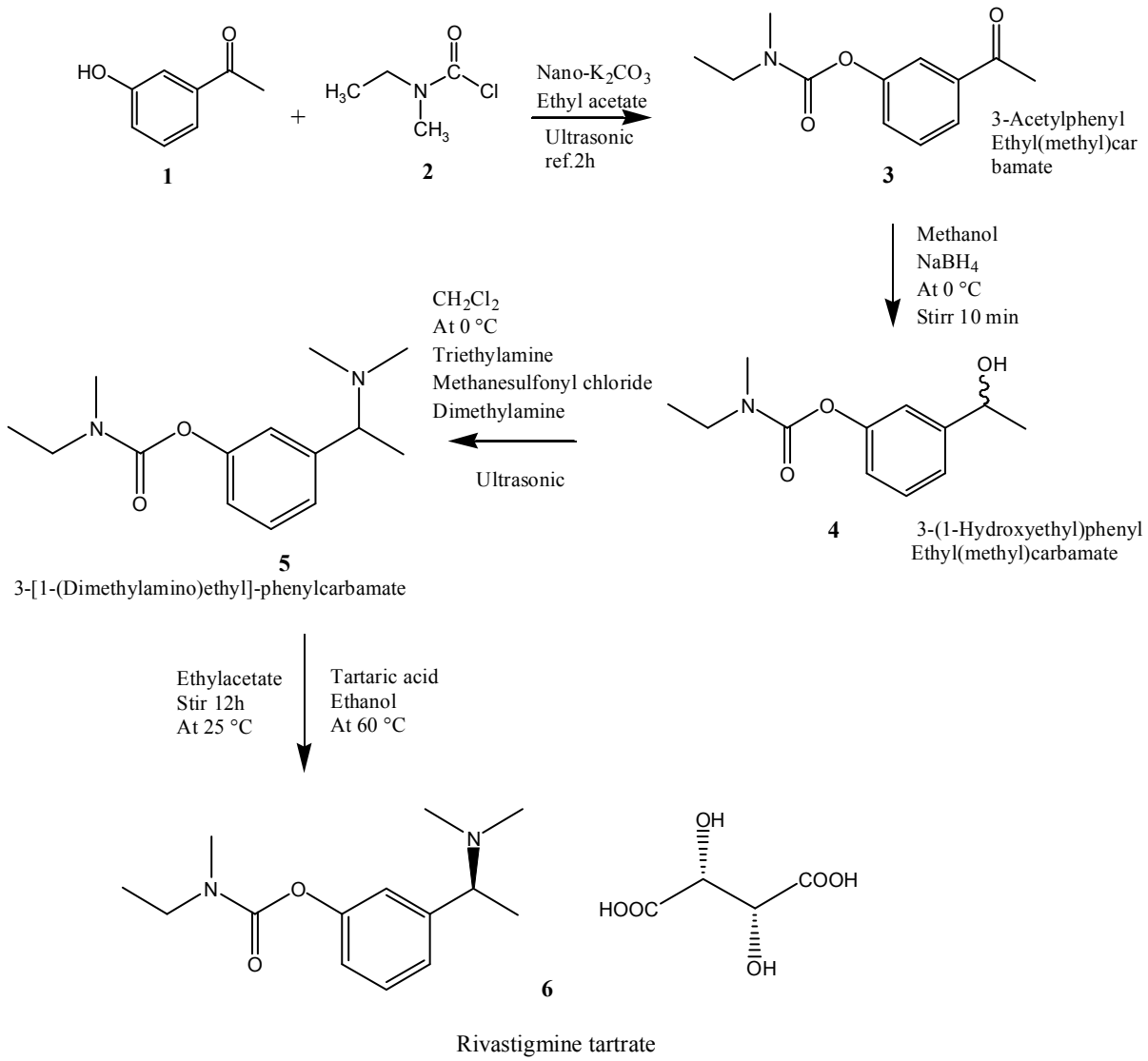

Figure 2. Synthesis of (S)-Rivastigmine tartrate.

Result and discussion

Our research group has been interested in the development of facile chemical processes for active pharmaceutical ingredients (API's). Although several methods for the synthesis of rivastigmine and phenylcarbamate derivatives have been reported, these methods suffer from limitations. Initial approaches have been developed viaresolution of recemate using chiral acids and transition metal catalysis. Recent approaches are based on lipase catalyzed kinetic resolution, chemoenzymatic asymmetric synthesis and asymmetric transfer hydrogenation [10-13]. In order to circumvent these difficulties we have devised a highly efficient enantioselective synthetic route.The route involved the condensation of m-hydroxyacetophenone(2) with 1.1 equiv N-ethyl-N-methyl carbamoylchloride in ethyl acetate in the presence of Nano-K_2CO_3 as base under ultrasonic irradiation togive 3. After simple aqueous workup and extraction, the crude 3 was subjected to

reduction with the catalystsodiumborohydride. Following distillationof the solvent EtOH and with an aqueous workup, the organicextracts were distilled into THF, and the solution was subjectedto mesylation with methanesulfonyl chloride in the presence ofEt_3N under ultrasonic irradiation. The resulting suspension was used directly in thesubsequent nucleophilic substitution with dimethylamine inportions at 0−20 °C to afford 5. It is noteworthy that purification of 5 was achieved by simple extraction and washingoperations under different pH values. Finally L-(+)-Tartaric acid was added to 5 in acetone. The mixture was heated to reflux. It crystallized dried easily. By the reported route, rivastigmine tartrate was obtained in 83% overall yield.

Conclusion

In summary, a high yielding stereoselective and short synthesis of (*S*)-Rivastigmine tartrate is described with an overall isolated yield of 83%. All the starting reagents and catalyst are inexpensive and commercially available. The reported strategy afforded under ultrasonic irradiation and in presence of Nano-K_2CO_3 via four steps, which (to the best of our knowledge) depicts the shortest and the most rapid method to enantiopure Rivastigmine tartrate reported to date.

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References

[1]. N. C. Berchtold and C. W. Cotman, *Neurobiol. Aging,* 3, 173 (1998).

[2]. J. Corey-Bloom, R. Anand and J. Veach, *Int. J. Geriatr. Psychopharm.,*2, 55 (1998).

[3]. M. Rosler, R. Anand, A. Cicin-Sain, S. Gauthier, Y. Agid, P. Dal-Bianco, H. B. Stähelin, R. Hartman and M. Gharabawi, *B. M. J.*, 7184, 633 (1999).

[4]. S. I. Finkel, *Clin. Ther.*, 7, 980 (2004).

[5]. M. Rosler, W. Retz, P. Retz-Junginger and H. J. Dennler, *Behav. Neurol.*, 4, 211 (1998).

[6]. M. Emre, D. Aarsland and A. Albanese, *N. Engl. J. Med.*, 315, 2509 (2004).

[7]. M.Emre, *CNS. Drugs,* 20, 748 (2006); M. R.Farlow, J. L. Cummings, *Am. J. Med.*, 120, 388 (2007); Y.Pan,X.Xianghua, X. Wang, *Br. J. Pharmacol*., 140, 907 (2003).

[8]. R. J. Polinsky, *Clin. Ther.*, 20, 634 (1998).

[9]. A.Gaitonde, M.Mangle, S.Pawar, *Chem. Abstr.*, 143, 77963 (2005); M. J. V.Garrido, A. M.Montserrat, M. J.Juarez, *Chem. Abstr.*, 146, 206113 (2007); D. W.Ma, Q. B.Pan, S.Pan, *Chem. Abstr.*, 146, 295621 (2007); H.Stepankova,J.Hajicek,S.Simek,*Chem. Abstr.,* 142, 6315 (2004).

[10]. A. A. Boezio, J. Pytkowicz, A. Cote, A. B. Charette, *J. Am. Chem. Soc.,* 125, 14260 (2003); M. Hu, F. L. Zhang, M. H. Xie, *Synth. Commun.*, 39, 1527 (2009).

[11]. K. Arunkumar, M. A. Reddy, T. S. Kumar, B. V. Kumar, K. B. Chandrasekhar, P. R. Kumar, M. Pal, *Beilstein J. Org. Chem.*, 6, 1174 (2010); M. Fuchs, D. Koszelewski, K. Tauber, J. Sattler, W. Banko, A. K. Holzer, M. Pickl, W. Kroutil, K. Faber, *Tetrahedron*, 68, 7691 (2012).

[12]. K. Han, C. Kim, J. Park, M. J. Kim, *J. Org. Chem.*, 75, 3105 (2010); R. Rao, M. P. Shewalkar, R. Nandipati, J. S. Yadav,M. Khagga, and D. B. Shinde,*SyntheticCommunications*, 42, 589(2012).

[13]. S. Puri, B. Kaur, A. Parmar, H. Kumar, *Ultrason. Sonochem.*, 16, 705 (2009); Y. Hu, Y. Zou, H. Wu, D. Shi, *Ultrason. Sonochem.*, 19, 264 (2012); J. T. Li, Z. P. Lin, *Ultrason. Sonochem.*,15, 265 (2008); J. T. Li, M. X. Sun, Y. Yin, *Ultrason. Sonochem.,*17, 359 (2010); J. Noei, A.R. Khosropour, *Ultrason. Sonochem.*, 16, 711 (2009); Y. Zou, H. Wu, Y. Hu, H. Liu, X. Zhao, H. Ji, D. Shi, *Ultrason. Sonochem.*, 18, 708 (2011).

[14]. G. Cravotto, P. Cintas, *Chem. Soc. Rev.,*35, 180 (2006).

[15]. P. Cintas, J.L. Luche, *Green Chem.*, 1, 115 (1999).

[16]. M. Nikpassand, M. Mamaghani, F. Shirini, K. Tabatabaeian, *Ultrason. Sonochem.,* 17, 301 (2010); T.J. Mason, *Ultrason. Sonochem.,* 14, 476 (2007); E. Kimmel, *Crit. Rev. Biomed. Eng.*, 34, 105 (2006); N.M.A. Rahman, T.S. Saleh, M.F. Mady, *Ultrason. Sonochem.*, 16, 70 (2009); E.K. Goharshadi, Y. Ding, N.M. Jorabachi, P. Nancarrow, *Ultrason. Sonochem.*, 16, 120 (2009).

[17]. Li, J. Z., Fan, S. M., Sun, X. F., Liu, S. *RSC Advances*,6, 3, 865 (2016).