

Ultrasonically Assisted Halogenation of Aromatic Compounds using Isoquinolinium Bound Hypervalent Chromium and Tetrabutylammonium Halides in PEG-600 Solutions under Acid Free and Solvent-Free Conditions†

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Received: 28 April 2018;

Accepted: 1 June 2018;

Published online: 30 June 2018;

AJC-18992

Isoquinolinium bound Cr(VI) reagents like isoquinolinium dichromate (IQDC) and isoquinolinium chlorochromate (IQCC) have been successfully accomplished as efficient reagents for oxidative halogenation of aromatic compounds using tetrabutylammonium halide (TBAX) as halogenating agents in aqueous polyethylene glycol (PEG-600) under acid free conditions. Tetrabutylammonium bromide (TBAB) has been used for bromination and tetrabutylammonium iodide (TBAI) for iodination. The halogenation reactions that occurred smoothly in 2 to 7 h under conventional conditions are accelerated magnificently under sonication with few minutes (25 to 70 min) of reaction time and fairly good yields. The reactions occurred at moderate temperature under mild and environmentally safe conditions with simple work up.

Keywords: Isoquinolinium dichromate, Isoquinolinium chlorochromate, Bromination, Tetrabutylammonium iodide, PEG-600.

INTRODUCTION

Halogenation of aromatic compounds is one the most important key areas of organic synthesis because organic halides can be easily transformed into other functional groups under mild conditions. In addition, organic halides are also used as important building blocks for the synthesis of life saving drugs and bioactive molecules [1-9]. A perusal of literature revealed that the two main preparatory routes *viz.*, direct halogenation and diazonium salt methods to obtain aryl halides [1-10]. Direct halogenation methods of aromatic compounds include the use of molecular halogen (X_2) either through thermal or photochemical routes. Friedel-Crafts method is also one of oldest and efficient methods of halogenation, in which Lewis acids are used as catalysts. Metal chlorides such as $FeCl_3$, $AlCl_3$ are the most popular metal chlorides in these reactions [1,2]. However, phenols, anilines and aromatic compounds with electron donating groups are known to undergo halogenation in the presence of halogens (molecular chlorine or bromine) even in the absence of Lewis acids to give halogenated products [3]. On the other hand, brominating mixture (a mixture of KBr and

$KBrO_3$) is also being used in presence of mineral acid for the generation of bromonium ion and there by effective bromination of aromatic compounds. In these protocols, large amount of acid waste is sent through the laboratory outlets after completion of the reaction, which may trigger environmental pollution. Several methods [4-15] have been tried in the past several years, which to address the environmental issues as well as to avoid the use of hazardous, toxic and corrosive Cl_2 and Br_2 . Recently, we have reported isoquinolinium chlorochromate (IQCC) and isoquinolinium dichromate (IQDC) as cost-effective oxidation catalysts to trigger halogenation of aromatic compounds [14,15] in presence of alkali metal halides (KCl, KBr and KI) and small amount of $KHSO_4$. The use of mineral acid is completely avoided in these protocols. On the other hand, polyethylene glycol (PEG) is considered as safe and eco-friendly reaction medium because of its low vapor pressure, non-flammability, non-hazardous, inexpensive and the ease of work up. In several cases, it is also used as an efficient phase transfer catalyst. In view of the foregoing striking features, PEG has been used in a large number of reactions in organic synthesis [16-24]. In a recent study, we have successfully explored aqueous polyethylene

†This work is a part of A. Sambashiva Rao's Ph.D. Thesis (PPCHE.030) submitted to Rayalaseema University, Kurnool, India.

glycols (PEG) as efficient reaction media for nitration of aromatic compounds using a variety of metal nitrates under acid free conditions [18]. Encouraged by these aspects coupled with the green chemistry guidelines [25], we have tried to develop a synthetic protocol, under acid-free and metal-free conditions, for halogenation of aromatic compounds using aqueous PEG-600 and tetrabutylammonium halide (TBAX).

EXPERIMENTAL

The chemicals used in this study were purchased either from Aldrich, Merck, Avra, Loba or Fluka. Melting points of the reaction products were recorded on BUCHI B-545 by placing capillary tube loaded with the solid product. Perkin Elmer FT-IR spectrometer is used to record infrared (IR) spectra, while Varian VNMRS-400 MHz spectrometer is for NMR spectra, with TMS internal standard. All the chemical shifts are reported as ppm values relative to CHCl_3 (7.26). ZAB-HS mass spectrometer is used to record the mass spectra of products with ESI ionization.

General procedure for halogenation of aromatic compounds in aqueous PEG-600 solution: Phenol (1 mmol, 10 mL) dissolved in 1M PEG-600, isoquinolinium dichromate (IQDC) or isoquinolinium chlorochromate (IQCC) reagent, and tetrabutylammonium halide (TBAX) (1.1 mmol each) were taken in a reaction flask and refluxed with constant stirring at about 25 to 30 °C, till the completion of reaction, as ascertained by thin layer chromatography. Then the contents of reaction were diluted with ethylacetate (10 mL) and separated from aqueous layer. Organic layer was then washed two to three times with 5 mL water and separated. Finally, the resultant mass is dried over sodium sulphate. The anhydrous ethylacetate layer was separated under reduced pressure to give crude product, which was further purified by column chromatography (silica gel, 100-200 mesh) using EtOAc-hexane (3:7).

For the separation and recyclization of PEG, aqueous mother liquor (reaction mixture of PEG-600 and water) was treated with ether because PEG is insoluble in ether. The aqueous layer obtained after the removal of ether, was then distilled directly at 100 °C to remove water and recover PEG-600. The recovered PEG-600 could be reused for consecutive runs.

General procedure for ultrasonically assisted halogenation of aromatic compounds in aqueous PEG-600 solution: Ultrasonically assisted halogenation of aromatic compounds is almost similar to the conventional reaction. The reaction vessel containing ingredients (TBAX, IQCC or IQDC, aromatic substrate, PEG-600 and solvent) was introduced into ultrasonic bath till the reaction is completed. TLC technique is used to monitor the progress of reaction. After confirming completion of the reaction, product was isolated following similar work-up procedure as mentioned above.

RESULTS AND DISCUSSION

In the present study, halogenation of phenols has been accomplished using TBAX in aqueous PEG-600 solution in the temperature range of 25 to 30 °C. Literature surveyed showed that PEG is soluble in water (due to hydrogen bonding) and also in aqueous alkaline media like NaOH, KOH or Na_2CO_3 . This aspect supports the contention that PEG exhibits mild acidic

properties in aqueous solutions. PEG produces non-ionic surfactants when coupled to hydrophobic molecules [22].

In order to have much more insight into the PEG interactions with isoquinolinium bound Cr(VI), the morphologies of phenol and PEG-600 are presented in Fig. 1 showed that sheet like structure embedded with flakes, which are slightly bigger in the case of PEG-600.

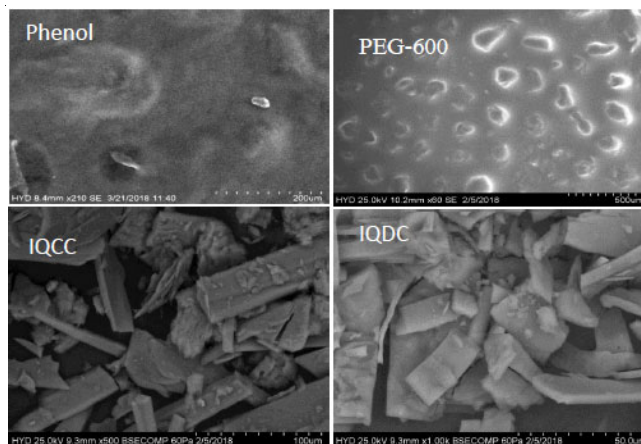


Fig. 1. Scanning electron microscope (SEM) images of reactants and PEG600

However, SEM images of IQCC and IQDC in presence of PEG-600 (Fig. 2) exhibited altogether different textures with bundles micro-belts, while SEM images of (IQCC + phenol) exhibited bundles of micro-size grains, spread over on the sheet. However, the morphology of IQDC and phenol mixture depicted bundles of flakes (belts) arranged one over the other. Interestingly, SEM images of (phenol + IQCC + PEG) and (phenol + IQDC + PEG) also shows nano-like structures, even though the morphology of (phenol + IQCC + PEG) is entirely different from that of (phenol + IQDC + PEG) with relatively smaller

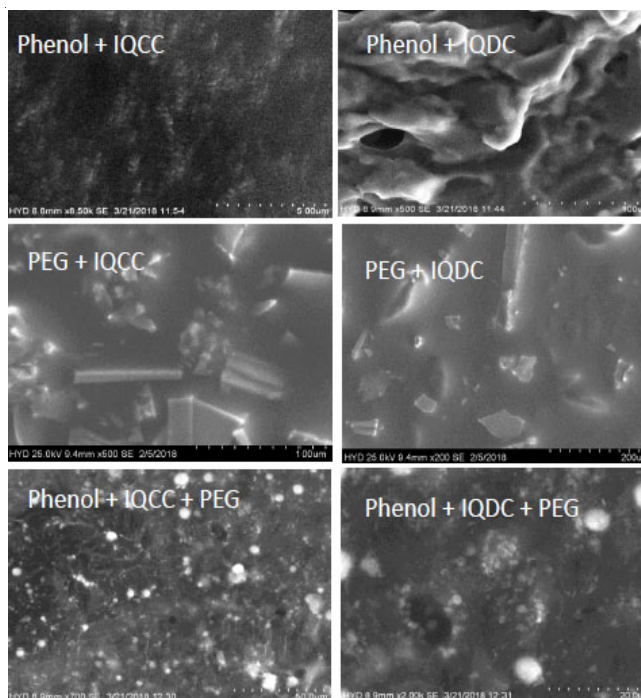
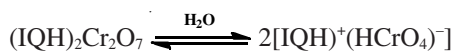


Fig. 2. Scanning electron microscope (SEM) images for PEG-600 interactions with reactants

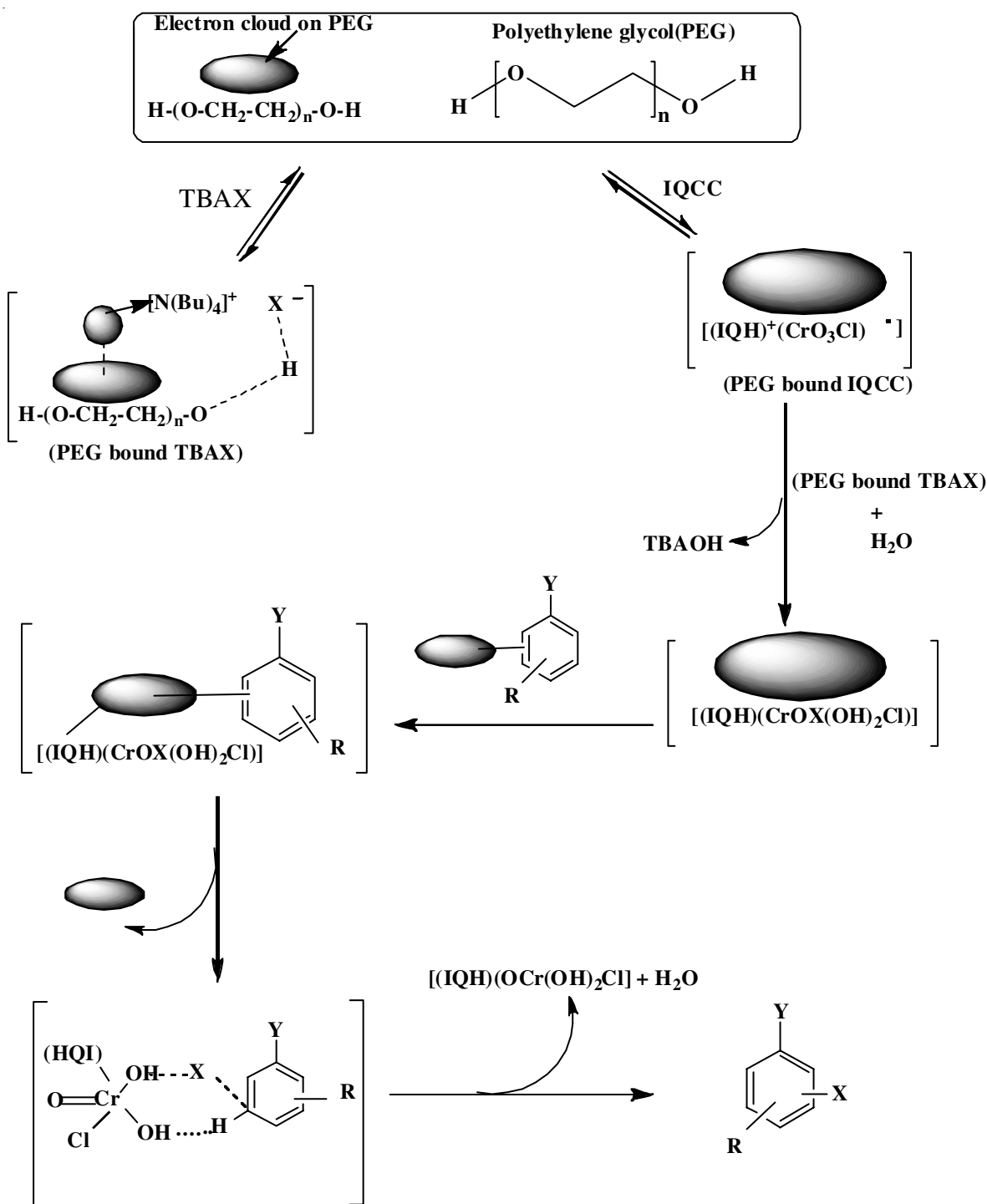
size nanostructures. Further, it is important to recall that initially IQDC hydrolyzes to afford active $[(\text{IQH}^+\text{HCrO}_4)^-]$ (IQ bound chromic acid species), according to the following equilibrium:



Almost, a similar type of mechanism is more likely in isoquinolinium chlorochromate (IQCC) initiated reactions through the formation of $[(\text{IQH}^+\text{CrO}_3\text{Cl})^-]$. The species thus formed may further react with TBAX to give $[(\text{IQH}^+\text{CrO}(\text{OH})_2\text{XCl})^-]$. Finally, the reaction between aromatic substrate and

$[(\text{IQH}^+\text{CrO}(\text{OH})_2\text{XCl})^-]$ yields halogenated aromatic substrate through a cyclic intermediate as shown in **Scheme-I**.

On the basis of the foregoing observations and discussions, it can be reasonably substantiated that PEG-600 bound structures also act like micro to nanoreactors as in the case of micelle catalyzed reactions and accelerate the halogenation of aromatic compounds in the presence of tetrabutylammonium bromide (TBAB) and iodination in presence of tetrabutylammonium iodide (TBAI). Interestingly, under sonication the reaction times are drastically reduced to few minutes followed by marginal yield enhancements all the protocols. Rate enhancements in



Scheme-I: Mechanism of IQCC triggered halogenation in PEG-600 medium

TABLE-1
ULTRASONIC EFFECTS OF BROMINATION IN PEG-600 UNDER ACID FREE CONDITIONS

Entry	Substrate	Product	TBAB/IQCC assisted bromination				TBAB/IQDC assisted bromination			
			Conventional		Sonication		Conventional		Sonication	
			RT (h)	Yield (%)	RT (h)	Yield (%)	RT (h)	Yield (%)	RT (h)	Yield (%)
1	Phenol	4-Bromo phenol	3.0	72	40	70	3.0	72	30	70
2	<i>o</i> -Cresol	4-Bromo-2-methylphenol	4.0	70	50	65	4.0	70	40	65
3	<i>p</i> -Cresol	2-Bromo-4-methylphenol	5.3	70	50	65	5.0	70	40	65
4	<i>m</i> -Cresol	4-Bromo-3-methylphenol	4.0	66	50	60	4.5	66	40	60
5	4-Bromo phenol	4-Bromo-2-bromo phenol	6.0	60	60	66	6.0	60	50	66
6	1-Naphthol	2-Bromo-1-naphthol	5.0	70	60	70	5.5	70	50	70
7	4-NO ₂ phenol	4-NO ₂ -2-bromo phenol	9.0	45	80	45	10.0	45	70	40
8	2-OH benzaldehyde	5-Bromo-2-OH-benzaldehyde	7.0	60	70	60	8.0	60	60	60
9	4-OH benzaldehyde	3-Bromo-2-OH-benzaldehyde	7.0	60	60	60	8.0	60	50	60
10	Toluene	2-Bromo toluene	7.0	60	50	70	7.0	60	40	70

TABLE-2
ULTRASONIC EFFECTS OF IODINATION IN PEG-600 UNDER ACID FREE CONDITIONS

Entry	Substrate	Product	TBAB/IQCC assisted iodination				TBAB/IQDC assisted iodination			
			Conventional		Sonication		Conventional		Sonication	
			RT (h)	Yield (%)	RT (h)	Yield (%)	RT (h)	Yield (%)	RT (h)	Yield (%)
1	Phenol	4-Iodo phenol	2.0	80	30	70	2.5	80	30	70
2	<i>o</i> -Cresol	4-Iodo-2-methylphenol	3.0	80	25	70	3.0	70	30	70
3	<i>p</i> -Cresol	2 Iodo-4-methylphenol	4.0	78	30	65	4.0	77	40	65
4	<i>m</i> -Cresol	4-Iodo-3-methylphenol	4.0	75	30	66	4.5	75	30	66
5	4-Bromo phenol	4-Iodo-2-bromo phenol	6.0	72	30	65	6.0	70	30	65
6	1-Naphthol	2 Iodo-1-naphthol	3.5	81	40	65	3.5	75	40	65
7	4-NO ₂ phenol	4-NO ₂ -2-iodo phenol	8.0	60	60	60	9.0	55	50	60
8	2-OH benzaldehyde	5-Iodo-2-OH-benzaldehyde	4.0	70	45	55	4.5	70	35	55
9	4-OH benzaldehyde	3-Iodo-2-OH-benzaldehyde	4.0	70	40	60	4.0	70	40	60
10	Toluene	2-Iodo toluene	6.0	65	50	60	4.0	66	50	60

sonicated reactions could be attributed to cavitation effects as mentioned literature reports [26-30]. At the same time faster rate accelerations are observed in CTAB/USAR protocols than in TX-100/USAR protocols. These trends could probably indicate that electrostatic interactions outweighed non-electrostatic (hydrophobic) interactions on one hand, and cavitation effect arising from ultrasonic transmission through the reaction mixture [23-25]. During sonication, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size and they can then collide and/or violently collapse. Cavitation induces very high temperatures in the liquid and enhances mass transfer. All the products were characterized by IR, ¹H NMR, mass spectra and physical data with authentic sample and found to be satisfactory. Reaction times and yield (%) of the products obtained in these protocols are presented in Tables 1&2 are characterized by ¹H NMR and mass spectra. The use of IQCC or IQDC/tetrabutylammonium halide (TBAX) as halogenating agents afforded high yields of iodo compounds with complete regioselectivity under neutral and mild reaction conditions. Direct iodination of wide range of aromatic compounds substituted with electron donating groups such as methoxy, hydroxy or amino groups have been achieved with high regioselectivity under mild conditions in excellent yields. Data presented in Tables 1 & 2 further substantiate that reaction times for TBAB are less than TBAI, showing the selectivity of the reactions.

Conclusion

In summary, the oxidative halogenation of aromatic compounds using tetrabutylammonium halide (TBAX) as halogenating agents [tetrabutylammonium bromide (TBAB)] for bromination and tetrabutylammonium iodide (TBAI) for iodination in aqueous PEG-600 solution under acid free conditions have been successfully accomplished. Highly sluggish conventional halogenation reactions are accelerated highly significantly. Under sonication the reactions are enhanced with much more ease. The reactions occurred under mild and under environmentally safe conditions with simple work up at room temperature. It is therefore, believed that the present protocols are important contributions in the area of halogenation reactions that occurred under very mild conditions with a simple and clean workup.

REFERENCES

1. R.N. Boyd and R.T. Morrison, Organic Chemistry, Englewood Cliffs, Prentice Hall: New Jersey (1992).
2. U. Beck and E. Löser, Chlorinated Benzenes and Other Nucleus-Chlorinated Aromatic Hydrocarbons, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim (2012).
3. E.R. Atkinson, D.M. Murphy and J.E. Lufkin, *Org. Synth.*, **4**, 872 (1951).
4. V. Paul, A. Sudalai, T. Daniel and K.V. Srinivasan, *Tetrahedron Lett.*, **35**, 7055 (1994); [https://doi.org/10.1016/0040-4039\(94\)88224-X](https://doi.org/10.1016/0040-4039(94)88224-X).
5. J. Yousefi-Seyf, K. Tajeian, E. Kolvari, N. Koukabi, A. Khazaei and M.A. Zolfigol, *Bull. Korean Chem. Soc.*, **33**, 2619 (2012); <https://doi.org/10.5012/bkcs.2012.33.8.2619>.
6. Y. Liu and S. Zhou, *Org. Lett.*, **7**, 4609 (2005); <https://doi.org/10.1021/ol051659i>.

7. R. Johnsson, A. Meijer and U. Ellervik, *Tetrahedron*, **61**, 11657 (2005); <https://doi.org/10.1016/j.tet.2005.09.051>.
8. T.I. Richardson, C.A. Clarke, K.L. Yu, Y.K. Yee, T.J. Bleisch, J.E. Lopez, S.A. Jones, N.E. Hughes, B.S. Muehl, C.W. Lugar, T.L. Moore, P.K. Shetler, R.W. Zink, J.J. Osborne, C. Montrose-Rafizadeh, N. Patel, A.G. Geiser, R.J.S. Galvin and J.A. Dodge, *ACS Med. Chem. Lett.*, **2**, 148 (2011); <https://doi.org/10.1021/ml100220b>.
9. T.A. Khan, S. Kumar, C. Venkatesh and H. Ila, *Tetrahedron*, **67**, 2961 (2011); <https://doi.org/10.1016/j.tet.2011.02.043>.
10. S.N. Joshi, S.M. Vyas, H. Wu, M.W. Duffel, S. Parkin and H.J. Lehmler, *Tetrahedron*, **67**, 7461 (2011); <https://doi.org/10.1016/j.tet.2011.07.064>.
11. B. Kuotsu, E. Tiewsoh, A. Debroy and M.K. Mahanti, *J. Org. Chem.*, **61**, 8875 (1996); <https://doi.org/10.1021/jo961079m>.
12. A. Suzuki, *Pure Appl. Chem.*, **63**, 419 (1991); <https://doi.org/10.1351/pac199163030419>.
13. S. Patel and B.K. Mishra, *Tetrahedron*, **63**, 4367 (2007); <https://doi.org/10.1016/j.tet.2007.02.073>.
14. A.S. Rao, K.C. Rajanna, K.R. Reddy and S. Kulkarni, *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.*, **46**, 832 (2016); <https://doi.org/10.1080/15533174.2014.989596>.
15. K.C. Rajanna, A.S. Rao, I.E. Chakravarthi and K.R. Reddy, *Asian J. Chem.*, **30**, 167 (2018); <https://doi.org/10.14233/ajchem.2018.20963>.
16. J.M. Harris, N.H. Hundley, T.G. Shannon and E.C. Struck, *J. Org. Chem.*, **47**, 4789 (1982); <https://doi.org/10.1021/jo00145a041>.
17. S. Baj and A. Siewniak, *Appl. Catal. A Gen.*, **321**, 175 (2007); <https://doi.org/10.1016/j.apcata.2007.01.049>.
18. D.J. Heldebrant and P.G. Jessop, *J. Am. Chem. Soc.*, **125**, 5600 (2003); <https://doi.org/10.1021/ja0291311>.
19. J. Chen, S.K. Spear, J.G. Huddleston and R.D. Rogers, *Green Chem.*, **7**, 64 (2005); <https://doi.org/10.1039/b413546f>.
20. M. Kidwai, D. Bhatnagar, N.K. Mishra and V. Bansal, *Catal. Commun.*, **9**, 2547 (2008); <https://doi.org/10.1016/j.catcom.2008.07.010>.
21. (a) B.P. Bandgar, S.A. Patil, B.L. Korbadi, S.B. Bandgar and B.S. Hote, *Aust. J. Chem.*, **61**, 552 (2008); <https://doi.org/10.1071/CH08041>.
(b) B.P. Bandgar, B.L. Korbadi, S.A. Patil, S.B. Bandgar, H.V. Chavan and B.S. Hote, *Aust. J. Chem.*, **61**, 700 (2008); <https://doi.org/10.1071/CH08106>.
(c) S.S. Gawande, B.P. Bandgar, P.D. Kadam and S.S. Sable, *Green Chem. Lett. Rev.*, **3**, 315 (2010); <https://doi.org/10.1080/17518253.2010.486772>.
22. J. Dey and S. Shrivastava, *Langmuir*, **28**, 17247 (2012); <https://doi.org/10.1021/la303210f>.
23. B. Das, M. Krishnaiah, P. Balasubramanyam, B. Veeranjanyulu and D.N. Kumar, *Tetrahedron Lett.*, **49**, 2225 (2008); <https://doi.org/10.1016/j.tetlet.2008.02.050>.
24. K.C. Rajanna, V.S. Chary, M.S. Kumar, G. Krishnaiah, P. Srinivas, P. Venkanna, M. Venkateswarlu, K. Ramesh, K.R. Reddy and B. Suresh, *Green Chem. Lett. Rev.*, **8**, 50 (2015); <https://doi.org/10.1080/17518253.2015.1105309>.
25. S. Adimurthy, G. Ramachandraiah, A.V. Bedekar, S. Ghosh, B.C. Ranu and P.K. Ghosh, *Green Chem.*, **8**, 916 (2006); <https://doi.org/10.1039/b606586d>.
26. W.T. Richards and A.L. Loomis, *J. Am. Chem. Soc.*, **49**, 3086 (1927); <https://doi.org/10.1021/ja01411a015>.
27. T.J. Mason, *Chem. Soc. Rev.*, **26**, 443 (1997); <https://doi.org/10.1039/cs9972600443>.
28. V. Singh, K.P. Kaur, A. Khurana and G.L. Kad, *Resonance*, **3**, 56 (1998); <https://doi.org/10.1007/BF02836081>.
29. T.J. Mason and D. Peters, *Practical Sonochemistry: Power Ultrasound Uses and Applications*, Hoorwood Publishing, Chichester, edn 2 (2003).
30. H. Fillion and J.L. Luche, ed.: J.L. Luche, *Selected Experiments*, In: *Synthetic Organic Sonochemistry*, Plenum, New York, Chap. 9 (1998).