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Contrasting chemoselectivities in the ultrasound and microwave assisted bromination reactions of substituted alkylaromatics with *N*-bromosuccinimide

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Abstract—Ultrasound and microwave assisted bromination reactions of various alkylaryls with *N*-bromosuccinimide, either neat or in water, shows diverse chemoselectivity. Thus, ring substitution occurs in water with ultrasound, whereas with microwaves both side-chain α-bromination and ring substitution occur. With neat reactants, side-chain α-bromination predominates for microwave assisted reactions. In the presence of water the chemoselectivity with microwave-promoted bromination is similar to that observed using classical methods.

Although ultrasound and microwaves have a total different approach in promoting chemical reactions, both, separately or combined, increase reaction rates and give higher yields, cleaner products and, occasionally, better chemoselectivities, when compared to traditional heating methods.[1] Also, both techniques have been used in recent years as part of the trend in developing more environmentally friendly synthetic methods and especially those where, in many cases, water has been used to replace organic solvents. It has been shown experimentally that ultrasound provides optimal results with reactions that are believed to proceed through free-radical intermediates, while microwave irradiation is more suited to the promotion of polar reactions. In addition, there are a few examples where given reagents can lead to different main products when different energy sources are used. The synthesis of pure compounds with only one isomer present is very important in organic synthesis as also is the ability to predict which isomer will be produced. The Wohl–Ziegler bromination method in which *N*-bromosuccinimide (NBS) is used in polar or non-polar solvents has been of great importance since the 1940s.[2] However, this reaction was initially performed in organic solvents (CCl_4, hexane, methyl formate) using a radical initiator.[3] In 1980, Vögtle and co-workers showed that NBS reactions are solvent dependent and the lower the refractive index of the solvent, the more selective the reaction is towards the benzyl bromide product.[4] Aromatic nuclear bromination can occur when Lewis acids are present in a stoichiometric amount or in solvents with high dielectric constants.[5] During the last decade light, microwaves and ultrasound have been employed in combination with attempts to avoid organic solvents by performing the bromination under solvent-free conditions, in ionic liquids or in water.[6] While NBS is known to participate in many radical reactions such as the side-chain bromination of alkylaromatics using traditional heating in various organic solvents, it has also, for example, been employed with cleaning bath-sonication in methanol in the reaction with acetophenones in the presence of *p*-toluenesulfonic acid where an ionic mechanism has been implicated.[7] However, its application to electrophilic aromatic substitution is not extensive.[8]

Here we report a comparative study of the chemoselectivity of the bromination of various substituted alkylaromatics with NBS promoted by ultrasound

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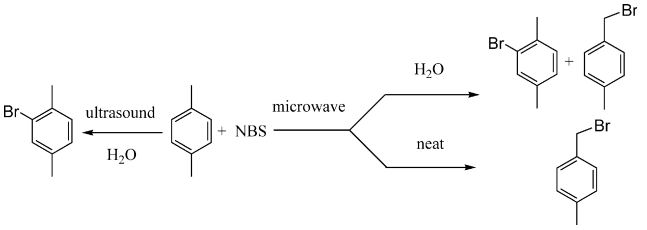
and microwaves both in water and with neat reactants.

Ultrasound bromination.[9a] It has been reported that *m*-xylene, when stirred with NBS in hexane in the presence of $HClO_4$ at room temperature for 10 days, reacts very slowly and affords 1-bromo-2,4-dimethylbenzene,[10] and that bromination of *o*-xylene with ultrasound using NBS at 25 °C in dry CCl_4 or AcOH gives 65–83% of the ring brominated product, 4-bromo-1,2-dimethylbenzene.[11] On the other hand, the ultrasound assisted NBS bromination of neat *o*-xylene gave 30% of the side-chain brominated product, 1-(bromomethyl)-2-methylbenzene, while no reaction was observed for toluene or *p*-xylene.[11] We have re-examined this reaction using water as the reaction medium. Although it has been reported[12] that the 'maximum cavitation' in water for ultrasound promoted radical reactions, occurs at 35 °C, no reaction occurred under our experimental conditions at that, or lower temperatures. For the xylenes (**1**–**3**, Table 3), no bromination was observed at 40 °C, whereas with mesitylene (**4**) the ring product was formed in 97% yield. However, at elevated temperatures (60–90 °C) the aromatic ring electrophilic substitution reaction of **1**–**3** proceeded with very good selectivity. The higher the temperature, the higher was the conversion to the ring mono-brominated product (Table 1). For **2** the conversion at 90 °C was higher (97%) than for **3** (88%) and **1** (55%). When no water was present in the sonication reaction with **3**, only side-chain substitution (61%) was observed. It should be mentioned that the reaction with conventional heating of **3** in water at 90 °C for 60 min afforded 23% ring mono-brominated, 27% side-chain mono-brominated and 20% di-brominated products, while without water 56% side-chain mono-bromination and 19% dibromination was observed. Ultrasound assisted bromination of methylnaphthalenes **5** and **6** using the same conditions as above, gave exclusively the corresponding ring brominated products. Cresols **7**–**9** gave a mixture of ring products, with no traces of α-bromination, except for **9** which afforded only a single ring product and traces of side-chain bromination. 1-Chloro-4-methylbenzene (**10**) and 1-*tert*-butyl-4-methylbenzene (**11**) afforded mainly side-chain bromination, accompanied by smaller amounts of 2-bromo-1-chloro-4-methylbenzene and (2-bromo-4-*tert*-butyl-1-methylbenzene and 2-bromo-1-*tert*-butyl-4-methylbenzene), respectively. Thus, in these latter reactions, it appears that the radical pathway predominates.

In order to see if our method could be applied to molecules with greater steric hindrance, we tested compounds that have been reported by us,[13] for example, 1,2-bis(1-ethylpropyl)benzene (**12**), 1,4-bis(1-ethylpropyl)benzene (**13**) and 1,2,4,5-tetrakis(1-ethylpropyl)benzene (**14**), but no evidence for conversion occurred even when the sonication time exceeded 3 h. For 2-(1-ethylpropyl)phenol (**15**) only two ring bromides 5-bromo-2-(1-ethylpropyl)phenol (47%) and 4-bromo-2-(1-ethylpropyl)phenol (13%) were obtained and no evidence for side-chain bromination was observed. All these observations could comply with the ionic mechanism that has been proposed,[10] for the halogenation of activated aromatics with NBS in acidic or non-acidic media. In addition, there were no differences in yields if the reactions were performed in the dark or in the presence of daylight or artificial light while sonicating and so there is no obvious synergistic effect.



Microwave bromination.[9b] In 2003 van Koten and coworkers reported the microwave assisted benzylic bromination by NBS of different methyl aryl halides in MeOAc in the presence of a radical initiator (AIBN),[14] while more recently, Goswami et al. reported the solid-phase side-chain bromination reaction of methyl-substituted heteroaromatic and aromatic compounds with no radical initiator using microwave irradiation.[15]

Our microwave experiments with NBS and different substituted arenes in the absence of any other reaction medium were performed without radical initiator. Some of these reactions were also performed in water. It should be noted that these reactions are very exothermic under our experimental conditions. With 250 W microwave irradiation in the absence of water, the reaction temperature rises slowly over about 2 min up to a certain temperature (ca. 100 °C) and then the reaction is triggered and the temperature jumps to about 150 °C within 10 sec. Consistently, when the preselected temperature is between 100 and 160 °C, this has no significant role and the yields were similar (within 4%, Table 2). After this period, and for an extra 2 min no microwave energy is transferred to the closed reaction vessel. After a total reaction time of 4 min, the mixture was rapidly cooled to room temperature.

Xylenes were solely α-brominated in the absence of water with yields in the following order: **1** (62%) > **2** (56%) > **3** (50%) and only **2** exhibited some degree of ring substitution (1.5%). In the presence of water, however, **3** underwent almost equimolar ring (27%) and side substitution (32%). In the absence of water, **4** gave 42% α-bromination and 6% ring-bromination (Table 3). Interestingly, 1-methylnaphthalene, **5**, was also mainly

Table 1. Temperature dependent ring-bromination yield of the ultrasound assisted reaction of **3** with NBS

T (°C)	50	70	80	90
Yield (%)	—	77	86	97

Power (520 W), time (40 min).

Table 2. Preselected temperature and time independent side-chain bromination yield of the microwave assisted reaction of **3** with NBS

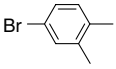
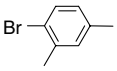
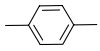
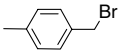
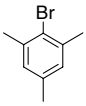
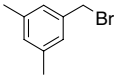
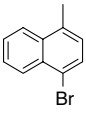
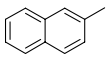
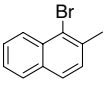
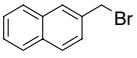
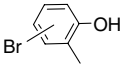
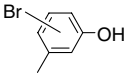
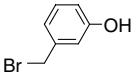
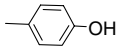
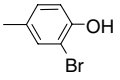
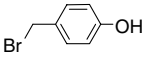
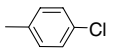
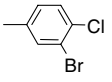
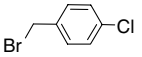
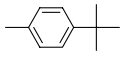
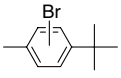
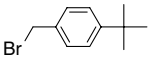
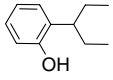
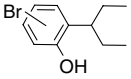
T (°C)	90	100	110	125	142
Yield (%)	2	53	54	54	56

Power (200 W), time (4–20 min).

side-chain brominated (53%) while 2-methyl isomer, **6**, was mostly ring brominated (54%). It should be noted that cresols **7**–**9**, when mixed with NBS reacted instantly, giving only ring substitution, so no microwave experiments were performed. The halogen-substituted substrate **10** and 1-*tert*-butyl-4-methylbenzene **11** gave mainly side-bromination. Compounds **12**, **13** and **14** were also tested under our microwave protocol and, as with the sonication experiments, no reaction occurred. Phenol **15** gave the same two ring products that were obtained by sonication.

Finally, with microwave irradiation we could also ring brominate the very bulky compound, **14**. The reaction

Table 3. Ultrasound (US) or microwave (MW) assisted bromination reactions of different alkylaryls with NBS[a]

No.	Starting material	Ring-bromination product	US yield[b] (%)	MW yield[b] (%)	Benzylic brominated product	US yield[b] (%)	MW yield[b] (%)
1			55	— (11)[c]		—	62 (51)[c]
2			97	1.5		—	56
3			88	— (27)[c] 23[d]		—	50 (32)[c] 27[e]
4			97[f]	6		—	42
5			94	18		—	53
6			88	54		—	17
7			86[g]	{82}[h]		—	
8			25[g]	{38}[h]		—	
9			43[g]	{17}[h]		—	
10			2	—		17	21
11			9	6		14	58
15			62	62			

[a] General experimental conditions: Ultrasound: temperature 90 °C, time 40 min, 520 W, in water. Microwaves: temperature 150 °C, time 4 min, 3.5 bar, 200 W, no water. Yields are only for monobrominated products. Some dibromination was observed by GC–MS in a number of the reactions although the products were not characterised.

[b] Yields were calculated from the GC of the products.

[c] Yields in ( ) are for microwave experiments performed in water.

[d] Conventional heating (H_2O, 110 °C, 60 min).

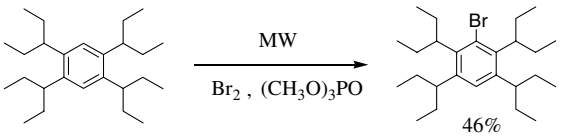
[e] Conventional heating (neat, 110 °C, 60 min).

[f] For **4**, temperature 50 °C.

[g] For **7**–**9**, time 10 min.

[h] Yields in { } are for reactions which took place simply on mixing the reagents and without any irradiation.

was performed with bromine in trimethyl phosphate and afforded 3-bromo-1,2,4,5-tetrakis(1-ethylpropyl)-benzene.[16]



We have studied the bromination reaction of various aromatic compounds with NBS under high-intensity ultrasound or microwave irradiation with or without water. From our results it is clear that, in water, ultrasound strongly favours ring substitution for aromatic molecules bearing simple alkyl or hydroxyl groups and that, in the absence of water, microwaves are selective for the side-chain bromination of the same molecules. In the presence of water, the microwave assisted reaction gives results similar to those using conventional heating and promotes both ring and side bromination. Further comparative studies could lead us to predict which high-energy technique and which conditions should be used for a given reaction.

Acknowledgements

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9. (a) *General experimental procedures*. Commercially available reagents were used without further purification. Compounds **12–15** are products of KERAS (keras-ta@eie.gr). Ultrasound experiments were carried out in a 250 ml sonochemical reaction vessel fitted with a thermometer, a reflux condenser and probe (length 254 mm, diameter 13 mm) and controlled by a 650 W ultrasonic processor Sonics and Materials. This processor allows the ultrasonic vibrations at the probe (titanium alloy) tip to be set at 90%. The system was operated in the nonpulse mode. In a typical reaction 0.32 g (3.0 mmol) of *p*-xylene and 0.54 g (3.0 mmol) of NBS were sonicated in 15 ml of water at 90 °C for 40 min. Hexane was added after sonication and cooling and the whole reaction mixture was transferred to a separation funnel. The organic layer was washed three times with 3×15 ml of water, dried over Na_2SO_4 and analysed by GC and GC–MS. For the NMR samples the solvent was evaporated prior to analysis. The comparative thermal reactions were carried out in 15 ml water at 90 °C for 40 min using the same reagent amounts as in the ultrasound reactions. The work-up and analysis of the reaction mixtures was as described above for the ultrasound assisted reactions; (b) Microwave-promoted experiments were carried out in the dark with a CEM Discover 300 W single mode microwave instrument. For the reactions without water, the closed vessels used were special glass tubes with self-sealing septa that controlled pressure with appropriate sensors on the top (outside the vial). The initial power was 200 W and when the preselected temperature was obtained it was automatically adjusted to maintain this temperature. The temperature was monitored through a non-contact infrared sensor centrally located beneath the cavity floor. Magnetic stirring was provided to assure complete mixing of the reactants. Under these conditions the pressure in the tubes never exceeded 4 bar. The 10 ml reaction vessels were charged in air with 0.32 g (3.0 mmol) of *o*-xylene and 0.54 g (3.0 mmol) of NBS. After the microwave irradiation was finished, the reaction mixture was cooled rapidly. The work-up and analysis was as described above for the ultrasound assisted reactions. When water (15 ml) was used, the microwave experiments were carried out in a 100 ml round-bottomed three-neck flask equipped with a magnet and a reflux condenser open to the air. The reaction vessel was submitted to microwave irradiation for 40 min in the cavity where the power (initially 100 W) was self-adjusted to maintain 90 °C. The quantities of reagents were the same as above. When the reaction time was reached, the mixture was cooled rapidly to rt. Work-up and analysis was as described above for the ultrasound assisted reactions.
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