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Metal Free Green Oxidation of Alkyl Substituted Aromatics with Aqueous *tert*-Butyl Hydroperoxide under Microwave Irradiation

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Abstract: 70% aqueous TBHP (*tert*-butyl hydroperoxide) with microwave irradiation is a green oxidation protocol for alkyl substituted aromatics. Methyl aromatics (toluenes and xylenes) can be oxidized directly to the industrially important carboxylic and dicarboxylic acids (phthalic acids). Addition of tiny amount of ionic liquid and simultaneous cooling improves the efficiency of these oxidations. For other alkyl substituted aromatics, ketones are obtained in good yields. The reaction medium is water. No additional organic solvent, metal based reagent or catalyst are needed.

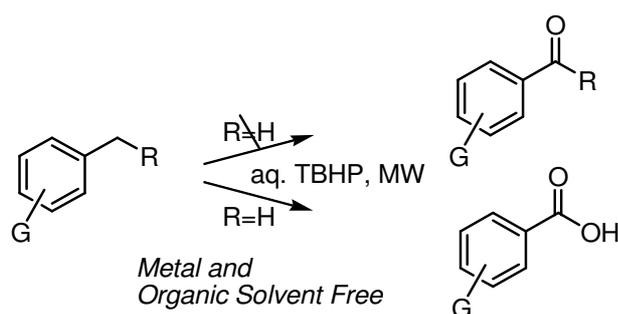
1. Introduction

Oxidation is the core technology to convert petrochemical based materials to commodity chemicals of higher oxidation state. For example, selective benzylic oxidations of alkyl substituted aromatics to ketones or carboxylic acids are fundamentally important laboratory and commercial transformations ¹. The oxidation products are important intermediates for the manufacture of high-value fine chemicals, agrochemicals, pharmaceuticals and high-tonnage commodities ². However, oxidation reactions also

present some of the greatest challenges to the environment. Many of the industrial oxidation processes involved heavy metals or corrosive reagents, and are high in energy consumption. For example, benzylic oxidations can be achieved by various transition metals based oxidizing agents such as permanganate and chromate. If molecular oxygen, hydrogen peroxide or hydroperoxide are used as the oxidants, metal based catalysts, either homogeneous or heterogeneous, are needed^{1,3}.

In recent years, there are considerable efforts to the development of environmentally conscious procedures for the production of carbon and aromatic feedstocks⁴. In these environmental benign processes, the uses of heavy metals should be avoided due to their toxicities, negative environmental impacts and the need to remove of residual metals from the reaction products. The uses of flammable organic solvents should also be reduced, if not totally abandoned, to reduce VOC emission. This type of green chemistry is believed to be the future of a sustainable chemical industry. In this article, we would like to outline a metal and organic solvent free directed oxidation protocol of alkyl substituted aromatic hydrocarbons to ketones or carboxylic acids using aqueous *tert*-butyl hydroperoxide (TBHP) as the oxidant and microwave as the energy source. The overall approach is outlined in scheme 1.

Scheme 1 Aqueous TBHP Benzylic Oxidation of Alkyl Substituted Aromatics



TBHP is an inexpensive oxidant widely used in industries⁵. As compared to concentrated hydrogen peroxide, TBHP is quite stable towards thermal decomposition. Actually, 70% aqueous TBHP constitutes a bulk organic chemical and has been certified for truck shipment in many countries.

Microwave assisted organic synthesis is a fast growing research area ⁶. The technique was first recognized as a method for reducing reaction time, commonly by orders of magnitude, and for clean reaction with increasing yields of products. In addition, it also provides opportunities for new reactions which are otherwise not feasible by conventional heating methods. An analogy had been made that microwave reactions could be the “Bunsen burners of the 21st century” ⁷.

2. Experimental

2.1 Materials

Unless otherwise noted, solvents and starting materials were obtained from commercial suppliers. All chemicals used were of reagent grade without further purification before use. ¹H NMR spectra were recorded on a JOEL JNM-EX 270 (270 MHz for ¹H) in CDCl₃ or DMSO-d₆. Chemical shifts were recorded in *ppm* (δ) relative to CHCl₃ on 7.26 and DMSO on 2.60. Experiments were conducted either in a CEM Discover Unit (300W, CEM Corporation, NC, USA) or a CHEMPOWER Reactor (800W, Shanghai, China).

2.2 Method. A

Experiments with 0.5-1.0 mmole of substrates were conducted using a CEM Discover Unit (CEM Corporation, NC, USA) in 10mL glass vessels sealed with rubber septa in stirred mode with or without simultaneous cooling. A targeted temperature together with a maximum microwave power (250 and 80W respectively for reactions without or with ionic liquid) was set. The targeted temperature was reached within a few minutes. During the course of the reaction, the microwave power as well as the pressure (60 to 240psi) varied.

2.2 Method B

Experiments with 0.5-1.3 mmole of substrates were conducted using a CHEMPOWER microwave reactor (Shanghai, China) in 10mL or 20 mL glass vessels sealed with rubber septa in stirred mode with or without simultaneous cooling. The highest power (750W) was set at the beginning so the targeted temperature can be reached within two minutes. With simultaneous cooling, the microwave power was

maintained at 160W to 400W during the course of the reaction. If there was no simultaneous cooling, the microwave power was comparatively lower (80~180W). During the reaction, the pressure in the vessel was maintained at 0.4 to 2.0 MPa.

2.3 NMR method for monitoring the oxidation of toluene

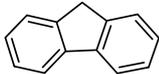
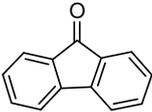
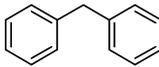
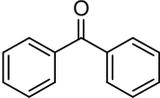
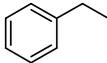
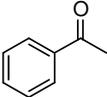
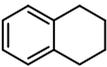
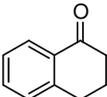
A sample of the reaction mixture was withdrawn and diluted with CDCl_3 . After treated with D_2O , the ^1H NMR (270 MHz) spectrum was recorded. The percentage conversion can be calculated from the integrations of the well resolved aromatic proton signals of benzoic acid (7.41-7.47, 7.54-7.57 and 8.05-8.08 ppm for the *meta*-, *para*- and *ortho*-protons respectively) and the methyl signal (2.35 ppm) of toluene.

3. Results and Discussion

3.1 Benzylic oxidation to ketones

Oxidation of methylene substituted benzylic aromatics to ketones (scheme 1, $\text{R}\neq\text{H}$) were first studied. When a mixture of fluorene and 10 equivalents 70% aqueous TBHP was irradiated with microwave in a sealed vessel for 10 minutes, almost quantitative yield of fluorenone was isolated (table 1). As a control experiment, simply reflux the same reaction mixture by conventional oil bath heating for 8 hours, only trace amount of fluorenone could be detected by TLC. Oxidation of another substrate with doubly activated benzylic position, diphenylmethane, also afforded benzophenone in high yield. For the mono-activated methylene units, ethylbenzene to acetophenone and tetrahydronaphthalene to alpha-tetralone, the oxidations under this green protocol also went smoothly. The results are summarized in table 1.

Table 1 TBHP Oxidation of Alkyl Substituted Aromatics to Ketones under Microwave Irradiation

substrate	conditions	MW power ^a	product	yield
	170°C, 10min	250-138W		98%
	180°C, 30min	245-146W		85%
	180°C, 30min	250-79W		77%
	170°C, 30min	240-97W		53%

^a CEM Discover Unit (300W), 0.5-0.6 mmol scale.

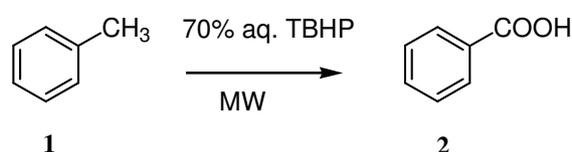
3.2 Oxidation of toluene and substituted toluenes

With the preliminary success in the oxidation of the benzylic methylene units, we then moved on to a more challenging task, oxidation of methyl substituted aromatics (R=H, scheme 1). Selective oxidation of methyl substituted aromatics to the corresponding carboxylic acids is of industrial importance and academic interest ^{2b,3}. In laboratory, various transition metals based oxidizing agents such as permanganate and chromate have been used. In industry, such oxidations are achieved by using heavy metals based catalysts at high temperature. For example, benzoic acid is produced commercially by oxidation of toluene with oxygen catalyzed by cobalt or manganese naphthenates.

Oxidation of toluene to benzoic acid was first used as the model study. The results are summarized in table 2. Each methyl oxidation requires three equivalents of the oxidant. With two folds excess of 70% aqueous TBHP (toluene/TBHP 1:6), toluene was converted 9.1% to benzoic acid under microwave irradiation in a 300W reactor at 160°C for 1 hr (entry 1, table 2). It is well documented that solvents

with high dielectric constants would enhance microwave absorption. When the oxidation reactions were carried out in *tert*-butanol, nitrobenzene or acetonitrile (entries 2, 3, 4) as the co-solvents, the percentage conversions were increased to 20-27%. We also explored the uses of other TBHP formulations such as TBHP in isooctane and toluene⁸. Oxidation can still take place but the results are inferior to the use of aqueous TBHP. As a control experiment, we carried out the oxidation at reflux (130°C) by conventional heating for 7 hours. No benzoic acid could be detected from the reaction mixture.

Table 2 Aqueous TBHP Oxidation of Toluene to Benzoic Acid under Microwave Irradiation



entry	TBHP (equiv.)	solvent	ionic liquid	temp. (°C)	simultaneous cooling	MW power	time (min)	conversion
1	2	/	/	160	no	250-133W ^a	60	9.1%
2	2	<i>t</i> -BuOH	/	160	no	250-85W ^a	60	20%
3	2	C ₆ H ₅ NO ₂	/	160	no	250-46W ^a	60	26%
4	2	CH ₃ CN	/	160	no	250-103W ^a	60	27%
5	2	/	2%	160	no	100-36W ^a	60	31%
6	6.6	/	2%	150	no	80-10W ^a	60	41%
7	6.6	/	2%	150	yes	80-49W ^a	60	71%
8	6.6	/	2%	150	yes	80-41W ^a	120	94%
9	6.6	/	1%	150	no	280-180W ^b	2	55%
10	5	/	1%	130	yes	400-240W ^b	20	74%
11	5	/	1%	130	yes	410-250W ^b	30	90% (71%) ^c

^a CEM Discover Unit (300W), 1 mmol scale. ^b CHEMPOWER Microwave Reactor (800W), 1.3 mmol scale. ^c Isolated yield.

Recently, it has been reported that addition of a small quantity of an ionic liquid can greatly increase the heating efficiency of a microwave reaction⁹. To improve the yield of toluene oxidation, the TBHP oxidation was carried out with 2% of 1-butyl-3-methylimidazolium tetrafluoroborate. The conversion was jumped to 31% as compared to 9.1% without the ionic liquid (entry 5 vs. 1). This result indicated that ionic liquid could replace the use of polar organic solvent. When the amount of TBHP was increased to 6.6 equivalents, the conversion was jumped up to 41% (entry 6).

With the uses of ionic liquids, the heating was so efficient that the reaction mixture could be easily overheated within a few seconds. Therefore, the microwave power cannot be set too high. In addition, the microwave power drop to a rather low level (around 10 to 30W) after the preset temperature had been reached. In order to maintain a reasonable level of microwave energy to sustain the reaction, we adopted the simultaneous cooling approach reported recently in literature¹⁰. A stream of compressed air or nitrogen at room temperature was passed over the reaction vessel during the microwave irradiation.

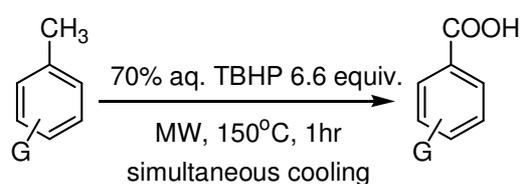
With the use of ionic liquid coupled with simultaneous cooling, the microwave power can be maintained within a reasonable level during the course of the reaction (1 hr). The percentage conversion was increased to 71% (entry 7). To drive the toluene oxidation to completion, the microwave reaction was run for 2 hrs with simultaneous cooling. Conversion up to 94% was achieved (entry 8).

Moving to a more powerful 800W microwave reactor, the efficiency of toluene to benzoic acid oxidation can be further improved. Using just 1% of ionic liquid and no simultaneous cooling, 55% conversion could be achieved *in just 2 minutes* at 150°C (entry 9). However, the heating efficiency was so high that the reaction pressure reached the machine's limit and the microwave power shut down automatically. Lowered the reaction temperature to 130°C and with simultaneous cooling, 74% conversion was achieved in 20 minutes (entry 10). Extended the reaction time to 30 minutes, conversion was up to 90% (entry 11). After simple work up and recrystallization, benzoic acid could be isolated in 71% yield.

With the more powerful microwave reactor, the reaction time can be shortened and the amount of ionic liquid and TBHP can be lowered to 1% and 5 equivalents respectively. Lowered the temperature of

the cooling gas to -20°C (from a tank of pressured liquid nitrogen), the efficiency of the TBHP oxidation was only slightly improved. The oxidation of substituted toluenes was also performed and the results were listed in table 3. It is obvious that electron withdrawing substituents slow down the oxidation process¹¹.

Table 3 Oxidation of Substituted Toluenes



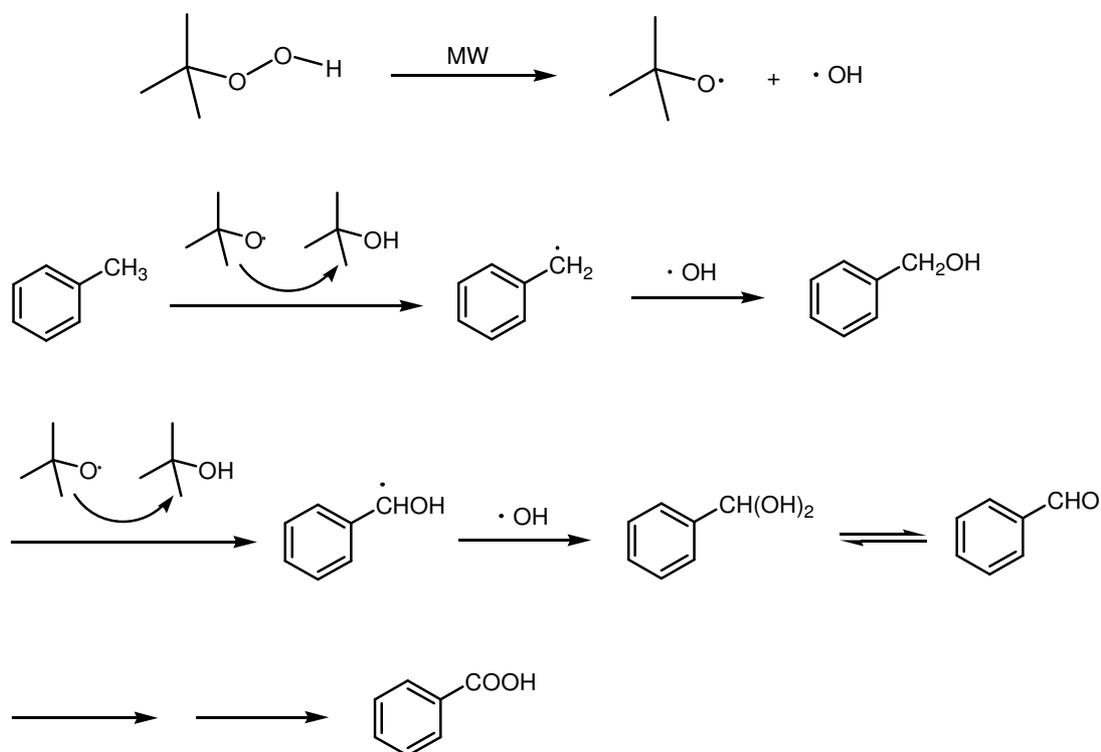
entry	G	ionic liquid	MW power ^a	conversion
1	<i>o</i> -Cl	2%	60-31W	46%
2	<i>m</i> -Cl	2%	70-15W	50%
3	<i>p</i> -Cl	2%	65-27W	57%
4	<i>p</i> -Br	2%	70-33W	51%
5	<i>o</i> -NO ₂	2%	75-34W	39%
6	<i>p</i> -OEt	/	70-30W	80%

^a CEM Discover Unit (300W)

4. Proposed mechanism

A proposed free radical mechanism of this microwave assisted direct oxidation is depicted in scheme 2. Upon microwave irradiation, TBHP is broken down into *t*-butoxide and hydroxyl radicals. Abstraction of a hydrogen radical from toluene gives a benzyl radical that combines with a hydroxyl radical to yield benzyl alcohol. Further oxidation could lead to benzaldehyde (or its hydrate) then benzoic acid. In fact, if we limited the amount of TBHP to 4 equivalents, tiny amount of benzaldehyde was detected in the ¹HNMR spectra of the reaction mixture.

Scheme 2 Mechanism of Microwave-Assisted TBHP Oxidation



5. Oxidation of xylenes

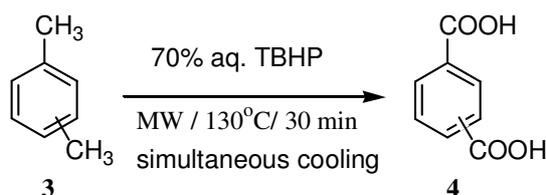
Oxidation of xylene isomers was then studied. The oxidized benzene dicarboxylic acids are important raw materials for many important commodities. For example, terephthalic acid (**4a**) is ranked as one of the top 50 industrial chemicals with a global demand amounts to 40 million tonnes per year and annual growth rate around 5 to 10 %. It is the key monomer of polyethylene terephthalate (PET), and PET is the common material for making soft drink bottles and other packaging resins. Textile and synthetic fibres such as polyesters (Terylene) are also made from terephthalic acids. On the other hand, isophthalic acid (**4b**) is also the monomer of several synthetic polymers and phthalic acid (**4c**) is the key precursor of many plasticizers.

In industry, these oxidations of xylene isomers are carried out under aggressive conditions. In the industrial production of terephthalic acid, *p*-xylene is oxidized by air in acetic acid at 200°C and a

pressure of 20 atm. The catalyst system is made of bromides of heavy metals and salts of cobalt and manganese. The reaction must be carried out in a titanium-lined reactor because the reaction mixture is highly corrosive. On the other hand, gas-phase oxidation of *o*-xylene to phthalic acid is carried out with fluidized-bed V₂O₅ based catalyst, and the oxidation of *m*-xylene to isophthalic acid employs a cobalt-manganese catalyst. In all these known oxidation processes of methyl aromatics, metal based oxidizing agents or catalysts are required.

Direct oxidation of the three xylene isomers (**3**) with 5 folds excess of 70% aqueous TBHP (each oxidation requires 6 equivalents of oxidant) under simultaneous cooling were carried out in a 800W microwave reactor. Results after 30 minutes irradiation are summarized in table 4. Terephthalic, isophthalic and phthalic acids (**4a,b,c**) were obtained in moderate yields from *p*-, *m*- and *o*-xylene respectively (table 4). The oxidation of xylenes is probably a stepwise process. Around 20% of toluic acids (methylbenzoic) were also obtained. To our surprise, small amount of benzoic acid was also detected. Using a less powerful 300W reactor, similar results were obtained except the reaction time required was 2 hours.

Table 4. TBHP Oxidation of Xylenes under Microwave Irradiation



xylene	phthalic acid	Microwave power ^a	yield crude (isolated)
<i>p</i> -CH ₃	terephthalic acid 4a	220-170W	53% (39%)
<i>m</i> -CH ₃	isophthalic acid 4b	380-200W	45% (30%)
<i>o</i> -CH ₃	phthalic acid 4c	210-150W	38% (29%)

^a CHEMPOWER Microwave Reactor (800W), 1.3 mmol scale, 2% ionic liquid.

In the case of *p*- and *m*-xylene, the oxidized benzenedicarboxylic acids (terephthalic **4a** and isophthalic **4b**) precipitated out from the reaction mixtures. This made isolations of these two products straight forward. After filtration and recrystallization, purified terephthalic and isophthalic acids can be obtained in moderate yields.

6. Conclusions

This is the first report of direct microwave assisted oxidation of alkyl aromatics with aqueous TBHP without involved any metal reagent. This oxidation of alkyl substituted aromatics to ketones, mono- and dicarboxylic acids is also an environmental friendly green chemical process. It is free of heavy metal with no added organic solvent. The only solvent involved is water¹² that comes with TBHP. Tiny amount of ionic liquid which is also viewed as a “green” reagent^{13,14} enhanced the oxidation efficiency. Finally, focused microwave is also a highly efficient “green” energy source as compared to conventional heating^{15,16,17}.

The oxidation of xylene isomers to the corresponding phthalic acids open up a green alternative to the synthesis of these economically important fine chemicals. Of course, in order to be commercially viable, the yields will need to be improved. Using a continuous flow reactor^{18,19,20} may be a possibility. Under a continuous flow system, the precipitated out diacid can be filtered off and the solution recycled back to the microwave reaction.

Acknowledgments

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