

## Solvent-Free Benzylic Oxidations Using Urea-Hydrogen Peroxide Complex (UHP) under Microwave Irradiation

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**Abstract:** Urea-hydrogen peroxide complex (UHP) has been found to be an efficient oxidizing agent for the oxidation of various alkyl benzenes/naphthalene/tetralin under microwave irradiation in solvent-free conditions.

**Key words:** alkylbenzenes, urea-hydrogen peroxide complex, benzylic oxidations, solvent-free conditions, microwave activation

Oxidations are important transformations in organic synthesis.<sup>1–3</sup> Laboratory scale liquid-phase benzylic oxidations are generally carried out with a large excess of chromium or manganese reagents.<sup>3</sup> The metal residues are environmentally undesirable and often provide problems during work up. Recently, nickel-catalyzed benzylic oxidation of toluenes was reported.<sup>4</sup> Other reagents which have been used for benzylic oxidations are ceric ammonium nitrate in aqueous acetic acid or in  $\text{HClO}_4$ ,<sup>5</sup> potassium bromate,<sup>6</sup> chromium trioxide in acetic anhydride,<sup>7</sup> selenium dioxide,<sup>8</sup> chromyl chloride,<sup>9</sup> silver(II)oxide in phosphoric acid,<sup>10</sup> potassium permanganate adsorbed on alumina<sup>11</sup> and 3,6-bis(triphenylphosphonium)cyclohexene peroxodisulfate.<sup>12</sup> Among these reported reagents, many are quite expensive, suffer from harsh reaction conditions or when used make use of solvents. The elimination of toxic and/or flammable organic solvents continues to be an area of current interest.<sup>13</sup> Thus, there is a need to develop procedures for benzylic oxidation, which use inexpensive oxidizing agents and minimize the use of organic solvents.

Among various oxidizing agents, hydrogen peroxide is emerging as a safe, economic and environment friendly reagent. Recently, hydrogen peroxide has been used for the oxidation of alcohols,<sup>14</sup> phenols,<sup>15</sup> amines<sup>16</sup> and nitriles.<sup>17</sup> Further, hydrogen peroxide in combination with claycop<sup>18</sup> or  $\text{MnO}_2$ <sup>19</sup> has been used as an oxidizing agent in solvent-free conditions.

Hydrogen peroxide is a mild oxidizing agent but it has associated problems. Urea-hydrogen peroxide complex (UHP), an addition compound of hydrogen peroxide and urea,<sup>20</sup> is an inexpensive, stable and easy to handle source of pure hydrogen peroxide which was introduced in 1993 by Heaney.<sup>21</sup> It has been reported for various oxidation reactions: for example UHP/trifluoroacetic anhydride

system<sup>22</sup> has been used for oxidation of organic sulfides to sulfones; oximes to nitroalkanes;<sup>23</sup> UHP-metal catalysts<sup>24</sup> for the oxidation of secondary amines to nitrones; UHP/DCC/ $\text{K}_2\text{CO}_3$ <sup>25</sup> for epoxidation of vinyl silanes; methyltrioxorhenium–UHP adduct for the regio- and stereoselective epoxidation of alkenes;<sup>26</sup> and UHP-DCC in methanol and ethanol for epoxidation of alkenes.<sup>27</sup>

Microwave (MW) assisted reactions have attracted much research interest<sup>28</sup> because of simplicity, milder reaction conditions and rapid synthesis of a variety of organic compounds.

In most of the reported oxidation reactions, UHP is used in combination with metal catalysts or with other reagents, which are either toxic or very expensive. In this paper, we wish to report the benzylic oxidations<sup>29</sup> using UHP alone under microwave irradiation<sup>30</sup> in solvent-free conditions. Our method is superior to other existing methods as there is no need of solvent, work up is simply reduced to treatment with dichloromethane, it makes use of easily available and inexpensive urea-hydrogen peroxide complex and leads to good yield of products.

Mestres et al.<sup>31</sup> recently reported benzylic bromination of toluenes using  $\text{H}_2\text{O}_2/\text{NaBr}$  in acidic conditions. We were also trying to carry out benzylic bromination of toluene with UHP/ $\text{NaBr}$  in acidic conditions in solvent-free conditions under microwave irradiation. To our surprise, no bromination, neither benzylic nor nuclear, takes place but oxidation of the aromatic methyl group to a carboxylic acid group takes place. However, in the case of alkanones,  $\alpha$ -bromination occurred with this reagent under the same conditions. The results are reported elsewhere.<sup>32</sup> So, we have extended our work for benzylic oxidations.

First, the oxidation of toluene was examined using UHP under different conditions. Under the same reaction conditions as for  $\alpha$ -bromination of alkanones (UHP/ $\text{NaBr}$ ), the product obtained was benzoic acid. We thought that UHP might be acting as oxidizing agent in the presence of sodium bromide. To our surprise, when oxidation of toluene was carried out with UHP without using any solvent/catalyst, under microwave irradiation, the same oxidation product, benzoic acid was obtained in 75% yield. Thus, UHP was acting as oxidizing agent alone, which makes the process highly economical and environmentally friendly.

Experimental conditions have been carefully monitored to optimize the reaction conditions. The amount of 15 mmol of UHP was required to oxidize 1 mmol of toluene. If the amount of UHP was increased, oxidation did take place but the reaction temperature rises rapidly and hence makes the process difficult to handle. In order to select the appropriate power level, we carried out the reaction of toluene at different power levels from 80 W to 800 W. The power level of 300 W was found to be the most promising as low power level gives low yield and prolongation of reaction time and higher leads to decomposition of the UHP complex thereby resulting in poor efficiency of the reagent. Oxidation of various substituted toluenes was examined by urea-hydrogen peroxide complex under microwave irradiation at 300 W. The results are summarized in Table 1.

Toluenes substituted at the 2- or 4-position by electron withdrawing groups such as nitro and carboxy groups were oxidized smoothly to the corresponding benzoic acids in excellent yields (entries 3, 4 and 9). Toluenes substituted by electron rich substituents (entries 2, 6, 7 and 8) also undergo oxidation efficiently. In the case of ethyl benzene, where there is a possibility of formation of acetophenone,<sup>4</sup> the reaction takes place exclusively for benzoic acid and no acetophenone was detected on TLC. The reagent works well for oxidation of naphthalene and tetralin to benzoic acid, where highly drastic conditions are generally required.

Finally, the oxidation of toluene and 4-nitrotoluene was carried out using thermostated oil-bath under the same conditions of time and temperature as for microwave-assisted method. Results are depicted in Table 2. It has been found that significantly lower yields were obtained using oil-bath heating than using microwave-assisted method under identical conditions of time and temperature. This is consistent with the observation that polar molecules gets more stabilized under MW irradiation as compared to

**Table 2** Comparison of Microwave Activation (MW) and Thermal Heating ( $\Delta$ ) in Case of Toluene and 4-Nitrotoluene (Power = 300 W)

Substrate	Method	Reaction temperature (°C) <sup>a</sup>	Time (min)	Yield (%)
Toluene	<b>MW</b>	<b>150–52</b>	<b>3</b>	<b>75</b>
	$\Delta$	152	3	0
	$\Delta$	152	20 <sup>b</sup>	65
4-Nitrotoluene	<b>MW</b>	<b>182–84</b>	<b>3</b>	<b>83</b>
	$\Delta$	184	3	0
	$\Delta$	184	40 <sup>b</sup>	67

<sup>a</sup> Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during microwave experiment and was approximate temperature range.

<sup>b</sup> Time at which maximum yield was obtained.

**Table 1** Microwave-Induced Oxidation of Alkylbenzenes with UHP under MW Irradiation (Power = 300 W)

Reactant	Product	Time (s)	Reaction temperature (°C) <sup>c</sup>	Yield (%) <sup>d</sup>
Toluene	Benzoic acid <sup>a</sup>	180	150–52	75
Ethylbenzene	Benzoic acid <sup>a</sup>	60	140–42	84
2-Nitrotoluene	2-Nitrobenzoic acid <sup>a</sup>	60	165–67	70
4-Nitrotoluene	4-Nitrobenzoic acid <sup>a</sup>	180	182–84	83
<i>o</i> -Xylene	Phthalic acid <sup>b</sup>	120	180–84	51
<i>o</i> -Cresol	Salicylic acid <sup>b</sup>	60	150–52	70
<i>m</i> -Cresol	3-Hydroxybenzoic acid <sup>a</sup>	60	130–32	68
<i>p</i> -Cresol	4-Hydrox benzoic acid <sup>a</sup>	160	141–44	70
4-Toluic acid	Terephthalic acid <sup>b</sup>	140	115–18	78
3-Toluidine	3-Aminobenzoic acid	60	160–62	75
4-Toluidine	4-Aminobenzoic acid <sup>a</sup>	50	125–27	79
Naphthalene	Benzoic acid <sup>a</sup>	120	120–22	79
Tetralin	Benzoic acid <sup>a</sup>	110	156–58	78

<sup>a</sup> Crystallized from EtOAc.

<sup>b</sup> Crystallized from EtOAc:petroleum ether.

<sup>c</sup> Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during microwave experiment and was approximate temperature range.

<sup>d</sup> Yield of isolated products.

non-polar ones.<sup>33</sup> The 4-nitrotoluene is more polar due to the presence of nitro group as compared to toluene and hence, more prone to microwave heating and thus, undergoes reaction faster than toluene. Under thermal conditions where polarity has no effect on the rate of reaction, 4-nitrotoluene undergoes reaction slower than toluene due to the deactivating effect of nitro group. Thus, microwave heating allows faster reaction and higher yields than oil-bath heating.

In conclusion, we have developed a simple, safe and economic method for oxidation of substituted toluenes, naphthalene, and tetralin. The procedure is environmentally friendly and is a useful alternative to existing methods.

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- (29) **General Procedure:** Substrate (1 mmol) and UHP (15 mmol) were added to a borosil beaker (50 mL). The mixture was stirred properly and then irradiated in a microwave oven for an appropriate time (Table 1) at 300 W (monitored by TLC). On cooling at r.t., the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined methylene extracts were washed with H<sub>2</sub>O and dried over anhyd Na<sub>2</sub>SO<sub>4</sub>. The product obtained after removal of the solvent under reduced pressure was crystallized from an appropriate solvent. UHP was prepared by recrystallizing urea in 30% H<sub>2</sub>O<sub>2</sub>.
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