



# CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; [www.cbijournal.com](http://www.cbijournal.com)

## Attempted side-chain bromination of *o/p*-hydroxyacetophenones using various brominating reagents: eco-friendly and convenient methods for nuclear bromination

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Received 28 December 2016; Accepted 21 February 2017

**Abstract:** Reaction of *o/p*-hydroxyacetophenones with  $\text{NH}_4\text{Br}-(\text{NH}_4)_2\text{S}_2\text{O}_8$  under aqueous grinding conditions,  $\text{NH}_4\text{Br}$ -oxone/methanol and  $\text{Zn-Br}_2/\text{H}_2\text{O}$  leads to nuclear bromination with the formation of mono and dibromo derivatives depending upon the amount of the reagents used. The results obtained from our investigations are in sharp contrast to the results of the reported work on side-chain bromination of such ketones. The study offers eco-friendly and convenient methods for nuclear bromination of *o/p*-hydroxyacetophenones.

**Keywords:**  $\text{NH}_4\text{Br}-(\text{NH}_4)_2\text{S}_2\text{O}_8$ , aqueous grinding conditions,  $\text{Zn-Br}_2/\text{H}_2\text{O}$ , nuclear bromination

### Introduction

$\alpha$ -Bromination of carbonyl compounds is an important transformation of organic synthesis as the resulting  $\alpha$ -brominated and  $\alpha,\alpha$ -dibrominated products are very useful intermediates.<sup>1,2</sup> For example,  $\alpha$ -bromoacetophenones and  $\alpha,\alpha$ -dibromoacetophenones are used for the  $\alpha$ -functionalization of carbonyl compounds,<sup>3-6</sup> construction of various heterocyclic structures<sup>7-10</sup> and small rings,<sup>11-13</sup> and preparation of unsaturated compounds.<sup>14-17</sup>  $\alpha$ -Bromocarbonyl

compounds are valuable building blocks in the synthesis of natural and non-natural products of significant biological interest.<sup>18-20</sup>

Generally,  $\alpha$ -bromo-arylalkanones are synthesized by the reaction of arylalkanones with bromine in an appropriate organic solvent or water.<sup>1,2,21-26</sup> Copper(II) bromide,<sup>3,27</sup> 1,4-dioxane bromooxonium bromide,<sup>28</sup> tribromoacetophenone<sup>29</sup> and *N*-bromosaccharin<sup>30</sup> have been used as brominating agents instead of health-hazardous bromine. In addition, several solid organic

ammonium tribromides, such as pyridinium,<sup>31</sup> phenyltrimethylammonium,<sup>32</sup> tetramethylammonium<sup>33</sup> and tetrabutylammonium tribromides<sup>34</sup> have also been used as selective brominating agents. Benzyltrimethylammonium tribromide<sup>35</sup> has been used for the selective synthesis of  $\alpha,\alpha$ -dibromoacetophenones. All these methods suffer from one or the other drawback such as use of expensive reagents and solvents, long reaction times and harsh conditions. So, recent studies have focused on the development of safer, economic and environmentally friendly selective methods for bromination. These developments include the use of NBS<sup>36-39</sup> under various conditions, ammonium bromide and ammonium persulfate in the presence of water under grinding conditions,<sup>40</sup> ammonium bromide and oxone in methanol,<sup>41</sup> dioxane–dibromide and silica gel in solvent-free conditions under microwave irradiation<sup>42</sup> and *in situ*-generated zinc bromide in water.<sup>43</sup>

In the course of an investigation into the development of a synthetic route to the synthesis of heterocyclic compounds such as thiazoles and imidazoles,  $\alpha$ -brominated and  $\alpha,\alpha$ -dibrominated *o*-hydroxy- and *p*-hydroxyacetophenones were required as intermediates. Based on the most recent reports dealing with the eco-friendly approaches for bromination of *o*-hydroxyacetophenone (**1**), *p*-hydroxyacetophenone (**2**) and 2,4-dihydroxyacetophenone (**3**), we attempted the synthesis of the required brominated hydroxyacetophenones (**4-8**) according to the methods described in these reports. However, the results obtained by us were found in sharp contrast to the reported results. Therefore, it was considered worthwhile to report herein the results of our investigation on bromination of **1**, **2** and **3**.

## Materials and Methods

**General:** Melting points were taken in open capillaries and are uncorrected. <sup>1</sup>H NMR spectra were recorded on a Bruker 400 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1800 IR spectrophotometer.

### Typical Procedures:

**Method 1: NH<sub>4</sub>Br-(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> grinding in presence of water.** A mixture of ketone **1** (1 mmol), ammonium bromide (2 mmol), and ammonium persulfate (2.5 mmol) moistened with ~10 drops of water was ground in a mortar by a pestle at room temperature for 15 minutes (condition i, Table, 1) and kept for an appropriate time until completion of the reaction. The reaction mixture was diluted with water. A solid precipitated upon dilution, was filtered off and recrystallized from ethanol to give pure product **9**.

**Method 2: NH<sub>4</sub>Br-oxone in methanol.** To a well-stirred solution of the ketone **1** (1 mmol), and ammonium bromide (2 mmol) in methanol, oxone (2.5 mmol) was added and the reaction mixture was heated to reflux for 120 min. (Table 2, condition iii). The reaction mixture was diluted with water. A solid precipitated upon dilution, was filtered off and recrystallized from ethanol to give pure product **9**. The reaction was also performed following the general procedure in a mixture of methanol and water instead of methanol only.

**Method 3: Zinc bromide catalyzed  $\alpha$ -bromination in presence of water.** To a well stirred mixture of ketone **1** (1 mmol), Zn dust (0.5 mmol), and distilled water (5 mL) in a round-bottomed flask (50 mL), bromine (1.5 mmol) was added. The reaction mixture was stirred at room temperature for the appropriate time

(Table 3, condition i). An exothermic reaction took place. On cooling, the solid obtained was filtered, washed with water and recrystallized from ethanol to give pure product **9**.

### Data for selected compounds

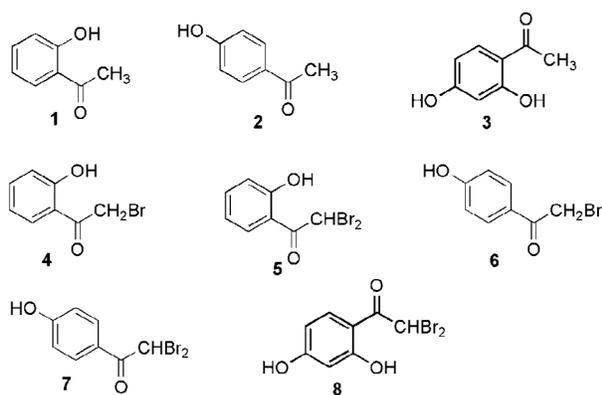
**3,5-Dibromo-2-hydroxyacetophenone (9):** IR (cm<sup>-1</sup>)  $\nu_{\max}$ : 3110 (O-H), 1645 (C=O), 1460 (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.66 (s, 3H, COCH<sub>3</sub>), 7.91 (s, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 11.92 (s, 1H, OH).

**3,5-Dibromo-4-hydroxyacetophenone (10):** IR (cm<sup>-1</sup>)  $\nu_{\max}$ : 3100 (O-H), 1660 (C=O), 1580 (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.56 (s, 3H, COCH<sub>3</sub>), 8.23 (s, 2 H, Ar-H), 6.40-6.65 (br, s, 1H, OH).

**3,5-Dibromo-2,4-dihydroxyacetophenone (12):** IR (cm<sup>-1</sup>)  $\nu_{\max}$ : 3400 (O-H), 1660 (C=O), 1460 (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.28 (s, 3H, COCH<sub>3</sub>), 8.23 (s, 1H, Ar-H), 11.92 (s, 1H, OH).

### Results and Discussion

Thus, we subjected ketones **1** and **2** to bromination under various conditions. The results are discussed in the following headings/subheadings based on the reagents/ conditions employed.



### Using bromides with oxidants

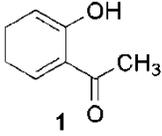
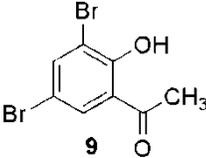
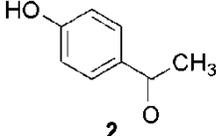
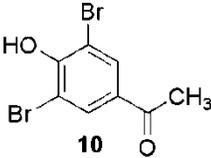
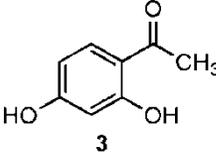
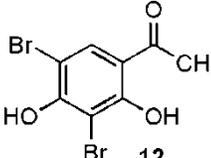
One of the most important reported methods for bringing about bromination, especially side-chain monobromination of aromatic ketones, involves oxidative bromination using bromides such as NH<sub>4</sub>Br with some oxidants.<sup>40,41</sup>

NH<sub>4</sub>Br-(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in presence of water under grinding conditions<sup>40</sup> (Method 1) An eco-friendly oxidative approach has been developed by Jakhar and Makrandi<sup>40</sup> for selective  $\alpha$ -bromination of ketones. Their method involves a combination of NH<sub>4</sub>Br-(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in presence of water under grinding, and is applicable to the bromination of various aromatic ketones (including *o/p*-hydroxyacetophenones) and heteroaryl methyl ketones.

In view of the operational simplicity and eco-friendly nature of the above mentioned oxidative bromination, we decided to synthesize bromoketones **4-8** following this approach. Accordingly, we first carried out the bromination of **1** by using the reported procedure for obtaining  $\alpha$ -bromo-*o*-hydroxyacetophenone (**4**). But the results obtained from our investigations were in sharp contrast to the results of Jakhar and Makrandi, and exclusive nuclear substitution with formation of 3,5-dibromo-2-hydroxyacetophenone (**9**) along with unreacted ketone was found. Using double the amount of reagent, the reaction afforded **9** in 90% yield. Further experiments using excess of brominating agent also yielded **9** exclusively. Aromatic substitution leading to the formation of 3,5-dibromo-4-hydroxyacetophenone (**10**) also took place when bromination of **2** was performed under similar conditions. The time required for grinding was, however, longer than that mentioned in the reported work (Table 1).

NH<sub>4</sub>Br-Oxone in methanol as a solvent (Method 2).<sup>41</sup>In a related development concerning the oxidative bromination of carbonyl compounds,

**Table 1.** Bromination of *o*-hydroxyacetophenone (**1**), *p*-hydroxyacetophenone (**2**) and 2,4-dihydroxyacetophenone (**3**) using NH<sub>4</sub>Br-(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (Method 1)

Substrate	Conditions: ratio of substrate / NH <sub>4</sub> Br/(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , reaction time (min) <sup>b,c</sup>	Product <sup>d</sup>	M.p.°C (lit M.p.)	Yield (%) <sup>a</sup>
	i) 1/2/2.5 (15 + 25) ii) 1/2/2.5 (60 + 25) iii) 1/4/5 (120 + 25)		110-1 (110-1) <sup>44</sup>	i) 47 ii) 85 iii) 90
	i) 1/2/2.5 (15 + 20) ii) 1/2/2.5 (60 + 20) iii) 1/4/5 (120 + 20)		180-1 (181) <sup>45,46</sup>	i) 20 ii) 80 iii) 89
	iv) 1/2/2.5 (15 + 25) v) 1/2/2.5 (60 + 25) vi) 1/4/5 (120 + 25)		170-3 (173-4) <sup>47</sup>	iv) 70 v) 80 vi) 84

<sup>a</sup> Yield of isolated pure product with respect to substrate. <sup>b</sup>Grinding time at room temperature.

<sup>c</sup>Time for which reaction mixture was kept at room temperature. <sup>d</sup>All the products were recrystallized from ethanol.

Nama *et al.* found that use of ammonium bromide in combination with oxone as an oxidant in methanol as a solvent is very effective for  $\alpha$ -bromination of ketones (Method 2).<sup>41</sup> Although this method is quite general for  $\alpha$ -monobromination of a variety of aralkyl ketones (acetophenones and acetophenones), cyclic/acyclic ketones, and  $\beta$ -dicarbonyl compounds, its major drawback is that the bromination of **1** using reported conditions is known to give mainly ring brominated product i.e., 5-bromo-2-hydroxyacetophenone (**11**). In an attempt to determine the effect of using two equivalents of the reagents, we carried out the reaction of **1** with two equivalents of the brominating mixture.

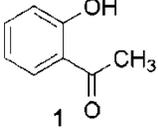
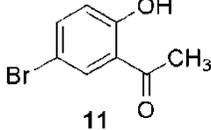
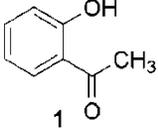
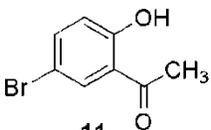
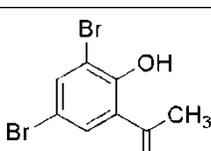
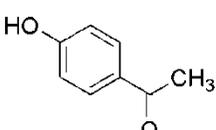
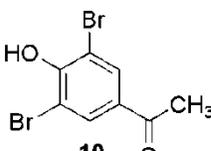
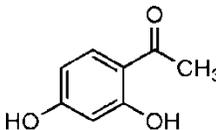
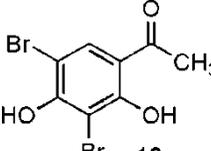
Interestingly, reaction led to the formation of ring dibrominated ketone **9**. However, using a mixture of methanol and water as solvent was found to give better results in terms of yields and eco-friendly nature of the reaction. The

dibromoketone **9** was also accessible by the bromination of **11** with one equivalent of the brominating agent. Similar results were obtained from *p*-hydroxyacetophenone and the reaction gave 3,5-dibromo-4-hydroxyacetophenone (**10**) in high yield (Table 2).

Using zinc bromide, *in situ* generated from Zn + Br<sub>2</sub> in water<sup>43</sup>(Method 3). Juneja *et al.*<sup>43</sup> have reported  $\alpha$ -bromination of various aliphatic and aromatic ketones by *in situ*-generated zinc bromide (from zinc and bromine) in water and claimed the versatility of this convenient method of a series of aryl alkanones containing electron-withdrawing and electron releasing groups including *o*- and *p*-hydroxy.

The most encouraging and advantageous feature of the method of Juneja *et al.* (Method 3) is that it is not only convenient in terms of execution and yields, but also highly selective for the synthesis of  $\alpha$ -monobromo and  $\alpha,\alpha$ -dibromo-

**Table 2.** Bromination of *o/p*-hydroxyacetophenones (**1**, **2**, **3**, and **11**) using ammonium bromide and oxone (Method 2)

Substrate	Condition: ratio of substrate/ NH <sub>4</sub> Br/oxone, reaction time(min)	Product <sup>d</sup>	M.p. °C (lit M.p.)	Yield (%) <sup>a</sup>
	i) 1/1/1.5, 30 <sup>b</sup> ii) 1/1/1.5, 60 <sup>c</sup>		63 (62) <sup>44</sup>	i) 58 ii) 50
	iii) 1/2/2.5, 120 <sup>b</sup>		110-1 (108-11) <sup>44</sup>	iii) 85
	iv) 1/1/1.5, 60 <sup>b</sup>		110-1 (108-11) <sup>44</sup>	iv) 91
	v) 1/2/2.5, 60 <sup>b</sup> vi) 1/2/2.5, 120 <sup>c</sup>		180-1 (181) <sup>45,46</sup>	v) 20 vi) 90
	vii) 1/2/2.5, 120 <sup>b</sup>		170-3 (173-4) <sup>47</sup>	vii) 70

<sup>a</sup>Yield of isolated pure product with respect to substrate. <sup>b</sup>Reflux temperature.<sup>c</sup>Room temperature.<sup>d</sup>All the products were recrystallized from ethanol.

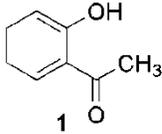
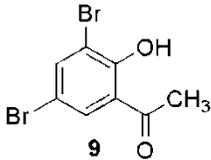
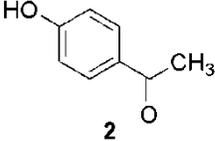
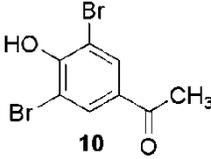
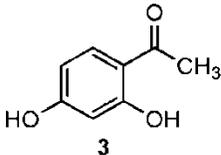
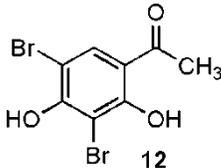
*o/p*-hydroxyacetophenones. Prompted by these observations, we attempted the synthesis of the target bromoketones following this procedure. But the results obtained from our investigations were again in sharp contrast to the reported results on mono- and di-bromination by Method 3, and led to almost exclusive nuclear substitution. For example, 3,5-dibromo-2-hydroxyacetophenone (**9**) was obtained in 90% yield from the bromination of *o*-hydroxyacetophenone according to the conditions described<sup>43</sup> for dibromination. Furthermore, using the condition of monobromination, the reaction also afforded **9** along with some monobrominated product

and starting ketone.

It should be pointed out that the general assumption in the bromination of aromatic compounds especially in phenolic compounds is that the presence of water in the bromination process favors nuclear substitution rather than side-chain substitution.<sup>44,45,48</sup> Obviously, reported work on the use of aforementioned reagents might be in error.

## Conclusion

**Table 3.** Bromination of *o*-hydroxyacetophenone (**1**), *p*-hydroxyacetophenone (**2**) and 2,4-dihydroxyacetophenone (**3**) using Zn + Br<sub>2</sub> in water (Method 3)

Substrate	Condition: ratio of substrate/ Zinc-dust/Br <sub>2</sub> , reaction time(min)	Product <sup>d</sup>	M.p. °C (lit M.p.)	Yield (%) <sup>a</sup>
	i) 1/.5/1.5, 60 <sup>b</sup> ii) 1/.75/2.5, 75 <sup>c</sup>		110-1 (110-1) <sup>44</sup>	46 90
	i) 1/.5/1.5, 60 <sup>b</sup> ii) 1/.75/2.5, 75 <sup>c</sup>		180-1 (181) <sup>45</sup> (179) <sup>46</sup>	45 92
	i) 1/.5/1.5, 60 <sup>b</sup> ii) 1/.75/2.5, 75 <sup>c</sup>		170-3 (173-4) <sup>47</sup>	80 90

<sup>a</sup>Yield of isolated pure product with respect to substrate. <sup>b</sup> Reflux temperature. <sup>c</sup> Room temperature. <sup>d</sup> products were recrystallized from ethanol.

In conclusion, the noteworthy features of the present study are as follows.

- i) The bromination of *o/p*-hydroxyacetophenones using NH<sub>4</sub>Br-(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> under grinding aqueous conditions (Method 1)<sup>40</sup> or NH<sub>4</sub>Br/oxone/methanol<sup>41</sup> or methanol + water as solvents, (Method 2) and Zn-Br<sub>2</sub>/H<sub>2</sub>O (Method 3),<sup>43</sup> exclusively leads to nuclear bromination.
- ii) The new methods for nuclear bromination of *o/p*-hydroxyacetophenone are eco-friendly and convenient in terms of execution, and offer superior alternatives to the existing methods.
- iii) By employing present reagents [NH<sub>4</sub>Br-(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> under grinding aqueous conditions, NH<sub>4</sub>Br/oxone/methanol or methanol + water and Zn-Br<sub>2</sub>/H<sub>2</sub>O], the twin advantages of avoiding liquid bromine and cost-effectiveness of used reagents are realized.

iv) Brominated hydroxyacetophenones, particularly *ortho* isomers **9**, **11**, and **12** are useful precursors for the synthesis of various heterocyclic compounds such as flavanones, hydroxyflavanones, flavones and flavonols.<sup>49</sup> Further work in this area is in progress and will be published elsewhere.

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