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### Microwave Assisted Oxidation of Benzyl Halides to Aldehydes and Ketones with 4-Hydroxypyridinium Nitrate Functionalized Silica Gel in Aqueous Media

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Aldehydes and ketones, available by numerous methods and from plentiful starting materials, are vital classes of chemicals which serve as precursors and intermediates for the preparation of such divergent products as drugs, vitamins and fragrances.<sup>1,2</sup> One of the methods for the synthesis of aldehydes and ketones is direct oxidation of organic halides.<sup>3,4</sup> The oxidation of benzyl halides into aldehydes is a well-known transformation in organic synthesis, although the oxidation of aliphatic halides to aldehydes is not common and is more difficult than the oxidation of benzyl halides.<sup>5,6</sup> Up to now, several methods have been developed for direct oxidation of halides to their corresponding carbonyl compounds. Dimethyl sulfoxide,<sup>7,8</sup> N,N-dimethyl-4-nitrosoaniline,<sup>9</sup> nitronate anion and Pd(PPh<sub>3</sub>),<sup>10</sup> pyridine N-oxides,<sup>11</sup> and other amine oxides,<sup>12</sup> chromate and dichromate systems,<sup>13</sup> silver nitrate,<sup>14</sup> pyrazinyl sulfoxides,<sup>15</sup> Mg-Al hydrotalcite,<sup>16</sup> V<sub>2</sub>O<sub>5</sub>,<sup>17</sup> NaIO<sub>4</sub>-DMF,<sup>18</sup> quinolinium chlorochromate,<sup>19</sup> H<sub>5</sub>IO<sub>6</sub> in  $[C_{12}mim]$  [FeCl<sub>4</sub>]<sup>20</sup> and amine oxides<sup>21–23</sup> have been used in the conversion of alkyl halides aldehydes and ketones. Recently NaOH-modified graphitic carbon nitride  $(g-C_3N_4)$ ,<sup>24</sup> nano-Fe<sub>3</sub>O<sub>4</sub>@L-arginine-CD-Cu(II),<sup>25</sup> (NH<sub>4</sub>)<sub>3</sub>[FeMo<sub>6</sub>O<sub>18</sub>(OH)<sub>6</sub>] with O<sub>2</sub><sup>26</sup> and amine-functionalized silica-coated iron-core nanoparticles<sup>27</sup> have been reported for the preparation of aldehydes and ketones from alkyl halides. However these procedures have some limitations, such as long reaction times, low yields, high temperatures, being harmful to the environment and difficult separation of the product from the reaction mixture. From an environmental and green chemistry viewpoint, there is a great need to develop new procedures with a broad substrate scope that will address the above-mentioned drawbacks for the direct oxidation of organic halides to their corresponding carbonyl compounds.

In this respect, leverage points for research concern the application of green oxidants, green solvents, or solvent-free processes, development of new catalytic systems, and the use of energy efficient heating methods. For example, microwave (MW) heating is one of the simplest but most effective ways to enhance energy efficiency and productivity in small-scale chemical production.<sup>28,29</sup>

Herein we wish to report the use of an eco-friendly heterogeneous oxidant based on 4-hydroxypyridinium nitrate functionalized silica gel for the oxidation of benzyl halides to the corresponding carbonyl compounds. The oxidant is a stable solid and can be

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Scheme 1. Preparation of oxidant.



**Figure 1.** FT IR spectra of a) 4-hydroxypyridine, b) SiO<sub>2</sub> and c) 4-hydroxypyridine functionalized silica gel.

prepared from the reaction of sodium 4-pyridinolate with an acidic activated silica gel which is then reacted with  $HNO_3$  (Scheme 1).

4-Hydroxypyridine $@SiO_2$  nanoparticles were synthesized (see Experimental section) and then characterized. Figure 1 shows the FT-IR transmission spectra in the range of 4000–400 cm<sup>-1</sup> at room temperature. The sharp peaks at 873 and 1069 cm<sup>-1</sup> were assigned to the Si–O-C stretching vibrations. This information was consistent with the formation of 4-Hydroxypyridine $@SiO_2$  nanoparticles.

The effect of microwave irradiation on the reaction times as well as the product yields was first established by reference experiments, after which it was sought to limit the amount of reagent in the mixture, and bring the reaction time under control. Table 1 indicates the results obtained for reactions done on 10 mmole scale.

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**Table 1.** Optimization of conditions in the reaction of benzyl chloride with 4-hydroxypyridinium nitrate functionalized silica gel under microwave irradiation in aqueous media.<sup>a</sup>



| Entry Substrate: Oxidant <sup>b</sup> |       | Total Irradiation Time (min)         | MW Power (W) | Conversion <sup>c</sup> (%) | Yield <sup>d</sup> (%) |  |
|---------------------------------------|-------|--------------------------------------|--------------|-----------------------------|------------------------|--|
| 1                                     | 1:3   | stirred at reflux conditions for 4 h | _            | 66                          | 61                     |  |
| 2                                     | 1:2   | 5                                    | 400          | 100                         | 98                     |  |
| 3                                     | 1:1.5 | 4                                    | 400          | 100                         | 98                     |  |
| 4                                     | 1:1.2 | 3                                    | 400          | 100                         | 98                     |  |
| 5                                     | 1:1.2 | 3                                    | 300          | 95                          | 91                     |  |
| 6                                     | 1:1.1 | 4                                    | 300          | 95                          | 91                     |  |
| 7                                     | 1:1.1 | 3                                    | 400          | 100                         | 98                     |  |
| 8                                     | 1:1.1 | 4                                    | 400          | 100                         | 98                     |  |
| 9                                     | 1:1   | 4                                    | 400          | 96                          | 93                     |  |
| 10                                    | 1:1   | 6                                    | 400          | 96                          | 93                     |  |
| 11 <sup>e</sup>                       | 1:1.1 | 40                                   | 600          | 57                          | 50                     |  |
| 12 <sup>f</sup>                       | 1:1.1 | 20                                   | 600          | 69                          | 63                     |  |

<sup>a</sup>Reaction conditions: benzyl chloride, oxidant and H<sub>2</sub>O (20 ml) under microwave irradiation.

<sup>b</sup>Molar ratio.

<sup>c</sup>Determined by GC.

<sup>d</sup>Isolated product (bezaldehyde).

<sup>e</sup>With 4-hydroxypyridinium nitrate in the absence of silica gel.

<sup>f</sup>With 4-hydroxypyridinium nitrate functionalized silica gel in the absence of  $H_2O$ .

The most desirable results (see Experimental section for full protocol) could be achieved on a 10 mmol scale when the ratio of substrate to oxidant was 1:1.1, in 20 ml of  $H_2O$  at 400 W microwave irradiation in two sequences for a total of 3 minutes (entry 7). In the presence of 4-hydroxypyridinium nitrate, instead of our new oxidant, or in the absence of water, more extreme conditions were required (entries 11 and 12) to achieve useful conversions to product. Our experiments indicated that reactive alcohols and amines such as benzyl alcohol and benzyl amine remained inert under these reaction conditions.

We found that a number of substituted benzyl bromides and benzyl chlorides were readily oxidized to the corresponding aldehydes and ketones in high yields in total irradiation times of 3-6 minutes under similar conditions. There were no signs of further oxidation of benzaldehydes to benzoic acids (Table 2, entries 1-12, 17-24). Prompt oxidation of the secondary halides into the respective ketones was noted with significant yields (entries 14, 25). Oxidation of cinnamyl chloride, was done to give cinnamaldehyde with high yields (entry 15). Alkyl halides remained inert under the conditions of this reaction (entries 16, 26). The product aldehydes were not oxidized into the respective carboxylic acids, even when a higher mole ratio of the supported oxidant was used. Extending the time did not lead to more reaction (entry 21).

Reusability of 4-hydroxypyridine functionalized silica gel was also investigated under the optimized conditions. Quantitative retrieval of 4-hydroxypyridine functionalized silica gel was performed following every experiment through four cycles after hot filtration. Activation was done by treatment with concentrated HNO<sub>3</sub>. Following this, benzyl

**Table 2.** Oxidation of benzyl halides with 4-hydroxypyridinium nitrate functionalized silica gel under microwave irradiation in aqueous media.



<sup>a</sup>All products were characterized by their physical and spectral data.<sup>31–33</sup> Reactions monitored by TLC. <sup>b</sup>No product was detected.

| Entry  | / Substrate <sup>a</sup>                           | Product | Reaction Conditions  | Yield (%) | Time               | Ref.       |
|--------|--|---------|--|-----------|--------------------|------------|
|        | R  | R       |  |           |                    |            |
| 1      | $\begin{array}{c} R = NO_2, \\ X = Br \end{array}$ |         | Benzyl bromide (5.85 mmol), Silver oxide<br>(2.93 mmol) and pyridine N-oxide (5.85 mmol) in<br>acctanitrile (10 ml) under nitragen   | 86        | Over nigh          | t 21       |
| 2      | R = H, X = Br                                      |         | Benzyl bromide (2 mmol), $H_2O_2$ (30%, 2 mL), ethanol (15 mL), and reflux.  | l 89      | 3 h                | 4          |
| 3      | R = H, X = CI                                      |         | Alkyl chloride (2 mmol), H <sub>2</sub> O <sub>2</sub> (30%, 2 mL), ethanol (15 mL), and reflux.   | 83        | 3.5 h              | 4          |
| 4      | $R = CH_3,$<br>X - Br                              |         | Benzyl bromide (2 mmol), H <sub>2</sub> O <sub>2</sub> (30%, 2 mL), ethanol<br>(15 mL) reflux  | 76        | 3 h                | 4          |
| 5      | X = Br, CI<br>$R = H, CH_3, OCH_3, X, NO$          |         | Benzyl halide (10 mmol), 4-hydroxypyridinium<br>nitrate functionalized silica gel (11 mmol) and<br>H <sub>2</sub> O (20 mL) and then NaOH (11 mmol) under<br>MW irradiation.             | 87-100    | 3-5 min            | b          |
|        |  |         |  |           |                    |            |
| 6<br>7 | $\begin{array}{l} X = Br \\ X = Br \end{array}$    |         | Reflux in 1:1 (v/v) acetonitrile/water mixture.<br>Benzyl bromide (5.85 mmol), Silver oxide<br>(2.93 mmol) and pyridine N-oxide<br>(5.85 mmol) in acetonitrile (10 mL)<br>under nitrogen | 85<br>82  | 1.8 h<br>Over nigh | 30<br>t 21 |
| 8      | X = Br, CI   |         | Benzyl halide (10 mmol), 4-hydroxypyridinium<br>nitrate functionalized silica gel (11 mmol) and<br>$H_2O$ (20 mL) and then NaOH (11 mmol) under<br>MW irradiation.                       | 98-100    | 3 min              | b          |

|  | Table 3. | Comparison of | present | method | with | some | reported | in | the | literature. |
|--|----------|---------------|---------|--------|------|------|----------|----|-----|-------------|
|--|----------|---------------|---------|--------|------|------|----------|----|-----|-------------|

<sup>a</sup>A number of positional isomers were investigated.

<sup>b</sup>Present work.

chloride was oxidized and yields of 98, 95, 93, and 91% were obtained under our optimized conditions. Tell-tale signals in the IR spectrum of the retrieved reagent were observed at 873 and  $1069 \text{ cm}^{-1}$  respective to Si-O-C stretching.

Comparison of the efficacy of 4-hydroxypyridinium nitrate  $@SiO_2$  for oxidation of benzyl halides under microwave irradiation in aqueous media was performed with some of those reported in the literature (Table 3).

In summary, 4-hydroxypyridinium nitrate functionalized silica is a reusable oxidant that functions better than some previously reported reagents, with higher yields and shorter reaction times, for the oxidation of benzyl halides to the corresponding carbonyl compounds under microwave irradiation in aqueous media. It is our hope that this versatile and convenient reagent will find wider use among organic chemists requiring this oxidative process.

#### **Experimental section**

Chemicals were purchased from Merck, Aldrich, or Fluka and used without further purification. Experiments were carried out in a closed vessel multi-mode Microsynth Milestone laboratory microwave oven. The melting points were determined on an Electrothermal 9100 apparatus. IR spectra were recorded on a Bruker Tensor 27 spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker 250 MHz spectrometer. For the data in Table 1, GC analysis of the reaction mixture was carried out using an Agilent 7890A GC instrument coupled to a flame ionization detector. Compounds were separated on a HP-5 capillary column (30 m, 0.25 mm, film thickness  $0.25 \,\mu$ m). The column temperature was kept at 90 °C for 3 min and programed to 230 °C at a rate of 5 °C/min. Injector and detector temperatures were 260 °C and the flow rate of helium as carrier gas was 1 mL/min. The reaction mixture in hexane was directly injected into the GC injector under the above temperature program in order to calculate the retention indices of substrate (benzyl chloride) and product. There were no signs of further oxidation of benzaldehyde to benzoic acid. All products are well-known compounds and they were identified by comparison of their physical and spectral data with those in the literature cited.<sup>31–33</sup> Representative original spectra data were submitted for editorial review. All yields refer to pure isolated products.

# General procedure for Preparation of 4-hydroxypyridine functionalized silica gel (4-hydroxypyridine@SiO<sub>2</sub>)

A fresh solution of 1.9 g of 4-hydroxypyridine (20 mmol) in 20 ml of NaOH (0.1 N) was added to 6 g silica gel (nano powder,  $99^+$ %, 600 m<sup>2</sup>/g) and was stirred at ambient temperature for 10 min; then it was activated by 12.8 ml of sulfuric acid (8.3 N); and the mixture was stirred at 40 °C, for 15 min until a milky solid was formed, which was collected, washed with 50 ml water and dried at 60 °C for 20 min.

### General procedure for preparation of 4-hydroxypyridinium nitrate functionalized silica gel (4-hydroxypyridinium nitrate@SiO<sub>2</sub>)

Concentrated HNO<sub>3</sub> (1.25 mL) was added to a solution of 7.9 g 4-hydroxypyridinium functionalized silica gel (containing 20 mmol 4-hydroxypyridine) in 40 ml of H<sub>2</sub>O within 2 min below 10 °C, then the mixture was stirred at ambient temperature for 15 min until a lemon-colored solid was formed. After filtration, the solid was dried at 90 °C for 1 h. The supported reagent could be kept for weeks in the dark without losing its activity. This synthesized reagent (0.1 g) was titrated by a standard solution of NaOH (0.1 N) to obtain its [H<sup>+</sup>] concentration which was 3.7 meq per gram of the powder.

## General procedure for the oxidation of benzyl halides with 4-hydroxypyridinium nitrate $@SiO_2$ under microwave irradiation

A mixture of benzyl halide (10 mmol) and  $H_2O$  (20 ml) was stirred, and then the mixture was added to 4-hydroxypyridinium nitrate functionalized silica gel (2.46 g, 11 mmol) and stirred. The reaction was done at ambient temperature for half the time indicated in Table 2 by microwave and then sodium hydroxide solution (0.440 g, 11 mmol, in 10 ml  $H_2O$ ) was added dropwise over a period of 5 min at room temperature with vigorous stirring. The mixture was irradiated again for the other half time indicated in Table 2. The progress of the reaction was monitored by TLC (silica gel, n-hexane: pet. ether (1:3) as eluent). When the reaction was complete, the reaction 182 👄 S. S. GHALEHBANDI ET AL.

mixture was cooled and extracted with diethyl ether  $(3 \times 20 \text{ ml})$ , washed with cold water, and dried over anhydrous sodium sulfate After filtration, the removal of solvent gave a crude product which was passed through a short silica gel column with n-hexa-ne:diethyl ether (1: 1) as solvent to afford the pure product. The retrieved regent (4-hydroxypyridine@silica gel) was activated by treatment with 1.25 ml of concentrated HNO<sub>3</sub> to provide 4-hydroxypyridinium nitrate@SiO<sub>2</sub>, then reused for the oxidation.

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