



## Oxidation of benzoin to benzil using sodium hydride

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### ARTICLE INFO

#### Article history:

Received 8 July 2010

Revised 6 September 2010

Accepted 9 September 2010

Available online 17 September 2010

### ABSTRACT

A highly efficient and eco-friendly oxidation of benzoin **1** to benzil **2** using sodium hydride has been developed.

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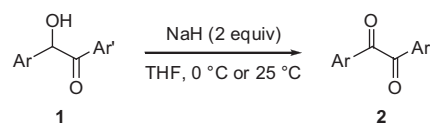
Benzils are used as building blocks for the synthesis of pharmaceuticals,<sup>1</sup> photoinitiators for the free-radical curing of polymer networks,<sup>2</sup> and precursors of porphyrins.<sup>3</sup> The direct oxidation of benzoin to benzil is a simple straightforward method and has been accomplished by using several oxidizing agents such as nitric acid,<sup>4</sup> ammonium nitrate-copper(II) acetate,<sup>5</sup> thallium(III) nitrate,<sup>6</sup> iodoxybenzene,<sup>7</sup> oxone-alumina,<sup>8</sup> bismuth(III) nitrate-copper(II) acetate,<sup>9</sup> iron(III) nitrate,<sup>10</sup> and *tert*-butyl hydroperoxide-titanium(IV) chloride.<sup>11</sup> Such an oxidation with molecular oxygen was catalyzed by trichlorooxovanadium,<sup>12</sup> nickel-aluminum hydrotalcite,<sup>13</sup> and a chiral cobalt complex,<sup>14</sup> Palladium-catalyzed oxidation of benzoin to benzil was achieved by using CsOH or K<sub>2</sub>CO<sub>3</sub> as a base.<sup>15</sup> Oxidation of benzoin was also performed on zeolite A without any oxidizing agent under solvent-free conditions and microwave irradiation.<sup>16</sup> Even though these reagents were employed for the oxidation of benzoin to benzil, most of the above oxidants are toxic and hazardous metal materials, thereby generating waste disposal problems after completion of the reaction.

In searching for a more efficient oxidation process, we have focused our attention toward the development of green reagent. Here, we report that sodium hydride can be used effectively for the direct conversion of benzoin to benzil under mild condition, which is of great value with respect to environmental and practical concerns. Sodium hydride is ordinarily employed as a strong base for the deprotonation of amides, esters, stannanes, and alcohols or as a reducing reagent for disulfides, disilanes, azides, and isoquinolines.

To develop a useful protocol, we studied the reaction of benzoin **1a** with 2.0 equiv of NaH at room temperature under a variety of conditions. First, the solvents were investigated by this process. In THF, the reaction can proceed effectively to provide the desired benzil product **2a** in high yield within a few minutes. In contrast,

the reactions were sluggish and gave lower yields in other solvents due to the side and the incomplete reactions: toluene, 32%; CH<sub>2</sub>Cl<sub>2</sub>, 30%; CH<sub>3</sub>CN, 19%; DMF, 18%; 1,4-dioxane, 15%. For further optimization of the reaction condition, the loading of sodium hydride was investigated. The results indicated that the amount of sodium hydride plays a paramount role in terms of the rate and the chemical yields. For example, less than 50% of benzil was obtained from benzoin in the presence of 1.0 equiv of NaH. The best chemical yield (>95%) of benzil was obtained when the reaction of benzoin was carried out using 2.0 equiv of NaH in THF at room temperature.

With the optimized reaction conditions in hand, we then explored the generality of this reaction for a variety of some symmetric and an unsymmetric benzoin derivatives possessing electron-donating and -withdrawing substituents on the phenyl ring of benzoin (Scheme 1 and Table 1). The oxidation of benzoin **1a** provided the product **2a** in 91% yield after 90 min (Table 1, entry 1). Gratifyingly, benzoin derivatives **1b–1d** bearing an electron-donating group, such as methyl or methoxy, at *para*- and *meta*-positions reacted with sodium hydride in THF to give the corresponding products **2b–2d** in good to excellent yields (70–88%) within 9–30 min (Table 1, entries 2–4). On the other hand, the trace amount of the desired products were observed when the chloro-substituent regardless of *meta* (**1e**)- or *para* (**1f**)-position on benzoin was employed at 25 °C, but the desired products **2e** and **2f** were obtained in 52% and 45% yields within 6 min at 0 °C, respectively (Table 1,



- a. Ar = Ar' = Ph  
 b. Ar = Ar' = 3-MeC<sub>6</sub>H<sub>4</sub>  
 c. Ar = Ar' = 4-MeC<sub>6</sub>H<sub>4</sub>  
 d. Ar = Ar' = 3-MeOC<sub>6</sub>H<sub>4</sub>  
 e. Ar = Ar' = 3-ClC<sub>6</sub>H<sub>4</sub>  
 f. Ar = Ar' = 4-ClC<sub>6</sub>H<sub>4</sub>  
 g. Ar = Ar' = 2-Thienyl  
 h. Ar = Ph, Ar' = 4-ClC<sub>6</sub>H<sub>4</sub>

Scheme 1. Oxidation of benzoin **1** to benzil **2** using NaH.

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**Table 1**  
Oxidation of benzoin **1** to benzils **2** using NaH

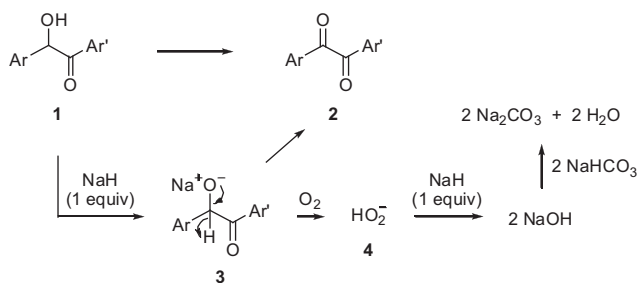
| Entry | Substrate <sup>a</sup> | Product <sup>b</sup> | Temp (°C) | Time (min) | Yield <sup>c</sup> (%) |
|-------|------------------------|----------------------|-----------|------------|------------------------|
| 1     | <b>1a</b>              | <b>2a</b>            | 25        | 90         | 91                     |
| 2     | <b>1b</b>              | <b>2b</b>            | 25        | 15         | 80                     |
| 3     | <b>1c</b>              | <b>2c</b>            | 25        | 30         | 88                     |
| 4     | <b>1d</b>              | <b>2d</b>            | 25        | 9          | 70                     |
| 5     | <b>1e</b>              | <b>2e</b>            | 25        | 15         | 5 <sup>d</sup>         |
| 6     | <b>1e</b>              | <b>2e</b>            | 0         | 6          | 52                     |
| 7     | <b>1f</b>              | <b>2f</b>            | 25        | 10         | 5 <sup>d</sup>         |
| 8     | <b>1f</b>              | <b>2f</b>            | 0         | 6          | 45                     |
| 9     | <b>1g</b>              | <b>2g</b>            | 25        | 15         | 90                     |
| 10    | <b>1h</b>              | <b>2h</b>            | 25        | 6          | 86                     |

<sup>a</sup> Substrates **1b**, **1d–1f** were prepared and characterized as described.<sup>17</sup>

<sup>b</sup> Products **2** were obtained and characterized as described.<sup>18</sup>

<sup>c</sup> Isolated yield.

<sup>d</sup> TLC yield.



**Figure 1.** Proposed mechanism for the oxidation of benzoin **1** to benzil **2** using NaH.

entries 5–8). Treating the heteroatom-containing benzoin derivative **1g** and the unsymmetric benzoin derivative **1h** with sodium hydride in THF gave the corresponding products **2g** and **2h** in 90% and 86% yields within 15 and 6 min, respectively (Table 1, entries 9 and 10).

To elucidate the role of oxygen in this process, we conducted the reaction of benzoin **1a** with sodium hydride in oxygen-free THF, which was introduced by vacuum transfer at  $-78\text{ }^{\circ}\text{C}$ . As a result, the moderate conversion (58%) was gained under this condition. It may seem obvious that oxygen plays an important role in the oxidation of benzoin.

The most important parameter influencing chemical yield in the reaction course is the controlled reaction time. It is noteworthy that the color change of the reaction mixture from navy solutions to yellow solutions represented the starting point of by-product formation. Another point is that the basic work-up (aqueous  $\text{NaHCO}_3$ ) was required to obtain high yield of the benzil after completion of the reaction.

The proposed mechanism for the sodium hydride-mediated oxidation of benzoin **1** to benzil **2** is illustrated in Figure 1. In the first step, 1 equiv of NaH leads to complete deprotonation of the hydroxyl group in the benzoin **1**. In the second step,  $\alpha$ -hydride of the resulting intermediate **3** is presumably transferred to molecular oxygen, leading to transient formation of hydroperoxide **4** and thus, simultaneously providing the desired benzil products **2**.<sup>15b</sup> Although the resulting hydroperoxide is not extremely reactive toward benzoin, however, it may potentially react with an additional equiv of NaH. Subsequently, 2 equiv of NaOH is released into the solution and then, it can be almost neutralized by 2 equiv of aqueous  $\text{NaHCO}_3$  added for work-up, thereby producing the desired product without any by-products.

In conclusion, we conducted a facile and simple method for the oxidation of benzoin to benzil using sodium hydride in good to excellent yields. Further studies of other related applications of this protocol are currently ongoing in our laboratories.

## Acknowledgments

This work supported by the NRF grant (No. 2009-0075000) to H.H. and the NRF WCU program (R31-2008-000-10029-0) to J.W.Y.

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- General procedure for the synthesis of benzoin 1b, 1d–1f*.<sup>19</sup> To a solution of benzaldehyde (15 mmol) in EtOH (8 mL) was added a solution of NaCN (6.3 mmol) in  $\text{H}_2\text{O}$  (1.5 mL). After stirring at reflux (80 °C) for 2 h, the reaction mixture was cooled to room temperature, concentrated in vacuo, and extracted with  $\text{CH}_2\text{Cl}_2$  and saturated aqueous  $\text{NaHCO}_3$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was purified by flash column chromatography to give **1b**, **1d–1f**. They were characterized by  $^1\text{H}$  NMR spectra, which are found to be identical to those reported previously: **1b**,<sup>14</sup> **1d**,<sup>14</sup> **1e**,<sup>20b</sup> and **1f**.<sup>14</sup> Benzoin **1a**, **1c**, and **1g** were purchased from TCI and **1h** was purchased from Aldrich.
- General procedure for the oxidation of benzoin 1 to benzil 2*. To a solution of benzoin **1** (0.5 mmol) in distilled THF (5 mL) was added NaH (60% dispersion in mineral oil, 1.0 mmol) at 0 °C. While stirring, the dark-blue solution was allowed to warm to room temperature. After stirring, until TLC analysis indicated complete consumption of the starting material, the reaction mixture was quenched with 0.1 M  $\text{NaHCO}_3$  (10 mL), extracted with EtOAc, and washed with brine. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue was purified by flash column chromatography to give **2**. All the benzil products were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, which are found to be identical to those reported previously.<sup>14,20</sup>
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