A Convenient and Practical Approach to α-Diketones via Reactions of Internal Aryl Alkynes with N-Iodosuccinimide/Water

Mingyu Niu,* Hua Fu,*a Yuyang Jiang,† Yufen Zhao*  

a Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. of China  
b Key Laboratory of Chemical Biology, Guangdong Province, College of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. of China  
Fax +86(10)62781695; E-mail: fuhua@mail.tsinghua.edu.cn

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A convenient and efficient approach to α-diketones is highly desirable because such compounds are versatile building blocks for a variety of chemical transformations such as the preparation of biologically active heterocyclic compounds, photoinitiators and chiral alcohols. Although several methods have been reported for synthesis of α-diketones, the oxidation of properly substituted internal alkynes is the most straightforward process. Previous oxidation methods include the use of potassium permanganate, DMSO or ozonolysis, or are peroxidant-based, transition-metal-catalyzed or acid-promoted. Practical applications of these methods is limited, however, since many are neither environmentally benign nor operationally efficient and involve hazardous transition-metals, high temperatures or cryogenic reaction conditions. Herein, we report a more convenient, practical and environmentally friendly one-pot method for the synthesis of α-diketones via reaction of internal alkynes with N-Iodosuccinimide (NIS) and water.

Initially, we chose diphenylacetylene and N-halosuccinimides (NCS, NBS, NIS) or I2 as model substrates with which to optimize the reaction conditions in an acetonitrile–water mixture (10:1 v/v). Room temperature reactions with NCS and NBS for 10 hours provided dichloroketone (3aCl) and dibromoketone (3aBr) in 18% and 17% yields, respectively, but no α-diketone product (benzil) was found. Extending this logic, we believed that NIS could thus be a better halogenation reagent than either NCS or NBS, so we attempted the reaction of diphenylacetylene with NIS in an acetonitrile–water mixture at 70 °C for 10 hours. Surprisingly, a 62% yield of benzil was obtained, with all the diiodoketone transformed into the α-diketone (entry 6). When iodine was used, the benzil was only obtained in 19% yield under the same conditions (entry 7). After optimizing the conditions, the oxidation of the internal alkynes to α-diketones was found to proceed best with NIS/water as the oxidant and acetonitrile as the solvent at 70 °C.

Table 1  Reactions of Diphenylacetylene and Water with N-Halo-succinimides or Iodine: Optimization of Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>NXS</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield of 2a (%)b</th>
<th>Yield of 3ax (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCS</td>
<td>MeCN–H2O</td>
<td>r.t.</td>
<td>trace</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>NBS</td>
<td>MeCN–H2O</td>
<td>r.t.</td>
<td>trace</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>NIS</td>
<td>MeCN–H2O</td>
<td>r.t.</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>NCS</td>
<td>MeCN–H2O</td>
<td>70</td>
<td>11</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>NBS</td>
<td>MeCN–H2O</td>
<td>70</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>NIS</td>
<td>MeCN–H2O</td>
<td>70</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>I2</td>
<td>MeCN–H2O</td>
<td>70</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: diphenylacetylene (0.25 mmol), N-halosuccinimide or I2 (0.5 mmol), MeCN (2 mL), H2O (0.2 mL).  
b Isolated yield.

As shown in Table 2, when the reaction was performed on a range of substrates, the corresponding α-diketones were obtained in various yields. Diarylketones showed higher reaction activity than monoarylacetylenes, and the internal alkynes containing electron-donating groups provided higher yields than those containing electron-withdrawing groups. For example, the yields of the corresponding α-diketones gradually decreased using substrates bearing increasingly electron-withdrawing groups.

Abstract: A convenient and practical approach to α-diketones via reactions of alkynes with N-iodosuccinimides/water at 70 °C has been developed.

Key words: α-diketones, alkynes, N-iodosuccinimide, convenient and practical, water

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### Table 2: Oxidation of Internal Alkynes with NIS/H₂O to α-Diketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
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<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td>2</td>
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<tr>
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<td><img src="image8.png" alt="Image" /></td>
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<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
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<td>65</td>
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<tr>
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<tr>
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<td><img src="image18.png" alt="Image" /></td>
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<tr>
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<td>11</td>
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<td><img src="image22.png" alt="Image" /></td>
<td>37</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: internal alkyne (0.25 mmol), NIS (0.5 mmol), MeCN (2 mL), H₂O (0.2 mL), 70 °C, 10 h.

<sup>b</sup> Isolated yield.
on the aryl ring (entries 1–4), while introduction of electron-donating groups on aryl ring could improve the yields of the α-diketones (see entries 5–7). Compound 1h, containing a Boc-protected amine, yielded the free amino α-diketone; presumably the Boc group was cleaved by HI generated during the reaction of the internal alkynes with NIS and water.

According to our experimental results and the reported literature, a possible reaction mechanism for the conversion of internal alkynes into α-diketones was shown in Scheme 1. Reaction of NIS with internal alkyne first provides B, leaving a succinimide anion A. Nucleophilic attack of water on B leads to an ortho-iodohydroxyl alkene intermediate C, whose isomerization gives the α-diketone. Iodination of D produces the dibromoketone (3aCl) and diiodoketone (3aBr) were obtained as shown in Table 1), whose hydrolysis provides the target product 2.

In summary, we have developed a convenient, practical and environmentally friendly method for the synthesis of α-diketones. The protocol uses NIS and water as the oxidant, acetonitrile as the solvent, and oxidation of the internal alkyne was performed at 70 °C. The direct functionalization of α-diketones by this inexpensive system (NIS/H2O) is of practical importance.

All reactions were performed under air. Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. Substituted alkynes are prepared via Sonogashira coupling. N-iodosuccinimide was prepared according to the reported procedure. NMR measurements were recorded with TMS or solvent resonance as the internal standard (1H NMR: TMS at δ = 0.00 ppm, CDCl3 at δ = 7.26 ppm; 13C NMR: CDCl3 at δ = 77.00 ppm).

### Synthesis of α-Diketones: General Procedure

Solid NIS (0.5 mmol, 113 mg) was added to a flask charged with internal alkyne (0.25 mmol) in MeCN (2 mL) and H2O (0.2 mL). The solution was stirred at 70 °C for 10 h then the resulting solution was cooled to r.t. and CHCl3 (10 mL) and aq Na2SO4 (1 M, 10 mL) were added. The separated organic phase was dried over anhydrous Na2SO4 and concentrated under rotary evaporation, and the residue was purified by column chromatography on silica gel (petroleum ether) (for compound 2h, a small amount of EtOAc was used to adjust polarity of solvent) to provide the pure α-diketone.

### 1,2-Diphenylethane-1,2-dione (2a)

- Light-yellow solid; mp 93–94 °C.
- 1H NMR (300 MHz, CDCl3): δ = 7.96–7.99 (m, 4 H), 7.63–7.69 (m, 2 H), 7.48–7.54 (m, 4 H).
- 13C NMR (75 MHz, CDCl3): δ = 130.6, 129.9, 129.8, 129.7, 128.9, 21.9.

### 1-(4-Chlorophenyl)-2-phenylethane-1,2-dione (2b)

- Light-yellow solid; mp 75–76 °C.
- 1H NMR (300 MHz, CDCl3): δ = 7.91–7.98 (m, 4 H), 7.65–7.70 (m, 1 H), 7.48–7.55 (m, 4 H).
- 13C NMR (75 MHz, CDCl3): δ = 193.9, 193.0, 141.6, 135.1, 132.7, 131.3, 131.2, 129.9, 129.4, 129.1.

### 1,2-Diketones

- **1-(2-Ethylphenyl)-2-phenylethane-1,2-dione (2e)**
- Light-yellow oil.
- 1H NMR (300 MHz, CDCl3): δ = 7.23–7.99 (m, 9 H), 3.10 (q, J = 7.2 Hz, 2 H), 1.30 (t, J = 7.6 Hz, 3 H).
- 13C NMR (75 MHz, CDCl3): δ = 194.8, 193.1, 164.9, 134.6, 133.9, 133.2, 131.5, 131.0, 130.0, 129.9, 125.9, 27.4, 15.4.

### 1-(2-Ethylphenyl)-2-phenylethane-1,2-dione (2e)

- Light-yellow oil.
- 1H NMR (300 MHz, CDCl3): δ = 7.23–7.99 (m, 9 H), 3.10 (q, J = 7.6 Hz, 2 H), 1.30 (t, J = 7.6 Hz, 3 H).
- 13C NMR (75 MHz, CDCl3): δ = 194.8, 193.1, 164.9, 134.6, 133.9, 133.2, 131.5, 131.0, 130.0, 129.9, 125.9, 27.4, 15.4.

### 1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (2f)

- Light-yellow oil.
- 1H NMR (300 MHz, CDCl3): δ = 7.96 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 7.9 Hz, 2 H), 7.80–7.83 (m, 1 H), 7.55 (t, J = 7.9 Hz, 2 H).
- 13C NMR (75 MHz, CDCl3): δ = 194.1, 191.4, 136.0, 134.5, 134.4, 133.7, 132.7, 132.5, 130.3, 128.9, 127.8, 127.4, 121.8.
- MS (EI): [M+] = 255.4.

### 1-(2-Bromophenyl)-2-phenylethane-1,2-dione (2c)

- Light-yellow solid; mp 139–140 °C.
- 1H NMR (300 MHz, CDCl3): δ = 8.36 (d, J = 8.9 Hz, 2 H), 8.17 (d, J = 8.9 Hz, 2 H), 7.98–8.01 (m, 2 H), 7.69–7.74 (m, 1 H), 7.55 (t, J = 7.9 Hz, 2 H).
- 13C NMR (75 MHz, CDCl3): δ = 196.7, 194.7, 147.5, 134.6, 133.9, 133.2, 131.5, 131.0, 130.0, 129.0, 125.9, 27.4, 15.4.

### 1-(4-Chlorophenyl)-2-phenylethane-1,2-dione (2d)

- Light-yellow solid; mp 139–140 °C.
- 1H NMR (300 MHz, CDCl3): δ = 8.36 (d, J = 8.9 Hz, 2 H), 8.17 (d, J = 8.9 Hz, 2 H), 7.98–8.01 (m, 2 H), 7.69–7.74 (m, 1 H), 7.55 (t, J = 7.9 Hz, 2 H).
- 13C NMR (75 MHz, CDCl3): δ = 194.8, 193.1, 164.9, 134.6, 133.9, 133.2, 131.5, 131.0, 130.0, 129.9, 125.9, 27.4, 15.4.
- MS (EI): [M+] = 255.4.

### 1-(4-Iodophenyl)-2-phenylethane-1,2-dione (2d)

- Light-yellow solid; mp 60–61 °C.
- 1H NMR (300 MHz, CDCl3): δ = 7.93–7.98 (m, 4 H), 7.61–7.67 (m, 1 H), 7.49 (t, J = 7.5 Hz, 2 H), 6.97 (m, 2 H), 3.88 (s, 3 H).
- 13C NMR (75 MHz, CDCl3): δ = 194.8, 193.1, 164.9, 134.6, 133.7, 133.2, 132.3, 129.8, 128.9, 126.1, 114.3, 55.6.
- MS (EI): [M+] = 244.2.

### 1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (2f)

- Light-yellow oil.
- 1H NMR (300 MHz, CDCl3): δ = 7.96 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 7.9 Hz, 2 H), 7.49 (t, J = 7.2 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 2.43 (s, 3 H).
- 13C NMR (75 MHz, CDCl3): δ = 194.7, 194.3, 146.2, 134.7, 133.1, 130.6, 129.9, 129.8, 129.7, 128.9, 21.9.
- MS (EI): [M+] = 224.3.
1-(4-Aminophenyl)-2-phenylethene-1,2-dione (2h)16
Yellow solid; mp 125–126 °C.

1H NMR (300 MHz, CDCl3): δ = 7.46–7.98 (m, 7 H), 6.64 (d, J = 8.6 Hz, 2 H), 4.25 (br s, 2 H).

13C NMR (75 MHz, CDCl3): δ = 195.5, 192.7, 152.9, 134.4, 133.4, 132.6, 129.9, 128.8, 123.1, 113.9.

MS (EI): m/z [M+] = 225.4.

1-Naphthyl-2-phenylethene-1,2-dione (2i)17
Light-yellow solid; mp 65–66 °C.

1H NMR (300 MHz, CDCl3): δ = 7.24–7.46 (m, 6 H).

13C NMR (75 MHz, CDCl3): δ = 129.7, 128.9, 128.0, 126.7, 69.5.

13C NMR (75 MHz, CDCl3): δ = 197.1, 194.9, 135.9, 135.1, 134.7, 134.1, 133.3, 130.9, 129.4, 129.0, 128.8, 128.6, 127.1, 125.9, 124.4.


1-(4-Methoxyphenyl)octane-1,2-dione (2j)18
Light-yellow oil.

1H NMR (300 MHz, CDCl3): δ = 6.95 (d, J = 8.2 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 114.2, 55.5, 38.8, 31.5, 28.8, 22.9, 22.4, 13.9.

13C NMR (75 MHz, CDCl3): δ = 123.2, 113.9.

13C NMR (75 MHz, CDCl3): δ = 132.6, 129.9, 128.8, 123.1, 113.9.

References
(b) De Kimpe, N.; Stanoeva, E.; Boekxens, M. Synthesis 1994, 427; and references therein.
(c) Held, I.; Xu, S. J.; Zippe, H. Synthesis 2007, 1185.

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