2-Iodoxybenzoic Acid Mediated Facile Conversion of 1,3-Diols to 1,2-Diketones by Oxidative Cleavage of the C–C Bond[1]

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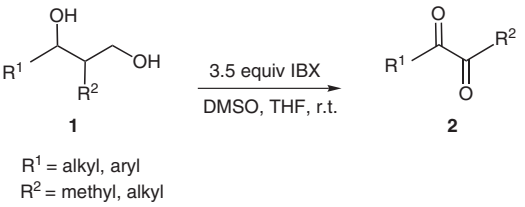
Abstract: 1,3-Diols undergo smooth oxidative cleavage of the C–C bond in the presence of 2-iodoxybenzoic acid (IBX) affording 1,2-diketones in excellent yields under mild conditions.

Keywords: 1,3-diol, 1,2-diketone, 2-iodoxybenzoic acid, oxidation, bond cleavage



Scheme 1

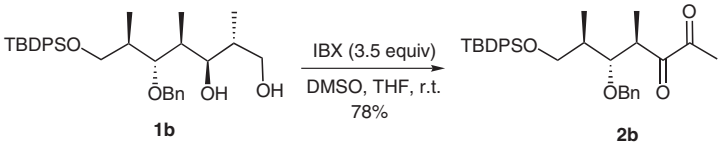
1,2-Diketones have received a great attention because of their wide application in organic synthesis.[2–8] 1,2-Diketones have also been found in many bioactive compounds, such as cytotoxic and antiviral hemigeran B and C.[9] Several approaches have been reported for the preparation of 1,2-diketones which include rearrangement of α,β-epoxy ketones,[10] oxidation of α-hydroxy ketones,[11] 1,2-diols,[12] vicinal dihaloalkenes,[13] alkenes or alkynes,[14] and epoxides.[15] Many of these methods involve expensive reagents, hazardous reaction conditions, and high temperatures which limits their use in large-scale synthesis. Hence, there is a need to develop a mild and efficient protocol for the preparation of 1,2-diketones.

Hypervalent iodine reagents have attracted increasing interest as oxidants in organic synthesis due to their mild, selective, and environmentally benign nature.[16] Among various hypervalent iodine reagents, 2-iodoxybenzoic acid (IBX) is a versatile oxidizing agent because of its high efficiency, easy availability, mild reaction conditions, and its stability to moisture and air. In recent years, 2-iodoxybenzoic acid has been used as a versatile reagent in mediating a wide array of transformations with far-reaching synthetic application.[17] However, there are no reports on the use of 2-iodoxybenzoic acid for the conversion of 1,3-diol into 1,2-ketones.

Herein we report, for the first time, the direct conversion of 1,3-diols **1** to 1,2-diketones **2** by oxidative cleavage of the C–C bond using 3.5 equivalents of 2-iodoxybenzoic acid in dimethyl sulfoxide at ambient temperature (Scheme 1).

In efforts toward the synthesis of biologically active molecule (+)-membrenone-C,[18] we attempted the selective oxidation of the primary alcohol in a 1,3-diol system in **1b**. We found that with an excess of 2-iodoxybenzoic acid, the 1,3-diol system underwent oxidative cleavage to afford a 1,2-diketone **2b** (Scheme 2).

Encouraged by the result obtained by the oxidation of **1b** to **2b**, several other 1,3-diol systems with aliphatic and aromatic substituents were oxidized with 3.5 equivalents of 2-iodoxybenzoic acid to yield the respective 1,2-diketones in good yields with a reasonably short reaction time. Noticeably, the yield of 1,2-diketone was consistent between a variety of substrates: simple aliphatic 1,3-diols, sterically hindered 1,3-diols containing variously protected hydroxy groups (Table 1, entries 1–4), and 1,3-diols substituted with aryl groups containing electron-withdrawing or electron-donating substituents (Table 1, entries 5–10). Interestingly cyclic 1,3-diol **1k** (Table 1, entry 11) afforded unsaturated diketone **2k** in 70% yield.[19] 2-Alkyl-substituted 1,3-diols with the alkyl as a group other than methyl under the same reaction conditions gave the 1,2-diketone in low yield, for example, 2-pentylbutane-1,3-diol gave octane-2,3-dione (**2a**) in <30% yield.



Scheme 2

SYNTHESIS 2006, No. 24, pp 4237–4241
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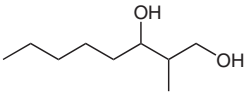
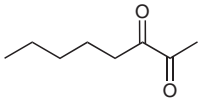
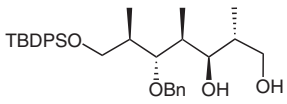
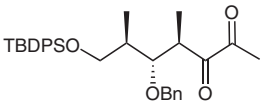
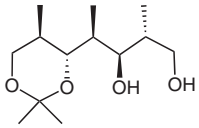
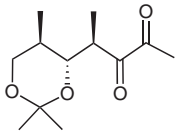
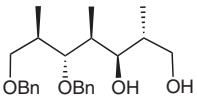
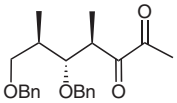
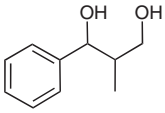
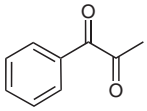
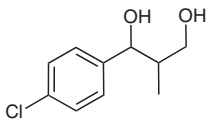
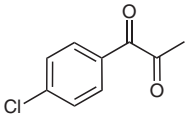
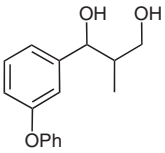
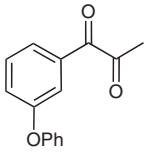
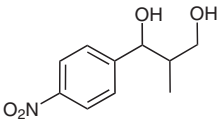
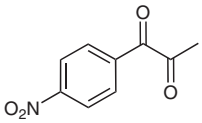
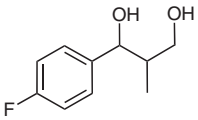
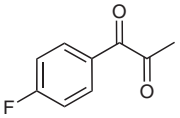
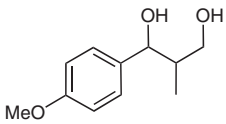
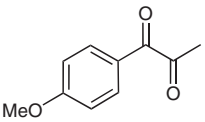
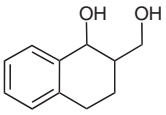
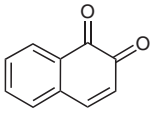
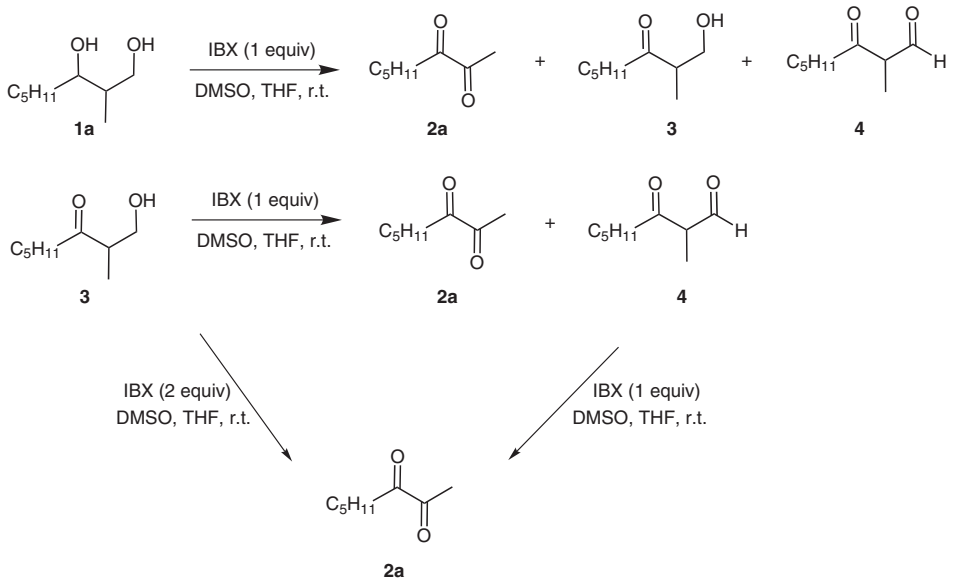
Table 1

Entry	Substrate		Product[a]		Time (h)	Yield[b] (%)
1		**1a**		**2a**	3.5	75
2		**1b**		**2b**	2.5	78
3		**1c**		**2c**	2.5	75
4		**1d**		**2d**	2.5	76
5		**1e**		**2e**	2.8	84
6		**1f**		**2f**	3.0	81
7		**1g**		**2g**	3.0	81
8		**1h**		**2h**	2.8	80
9		**1i**		**2i**	3.0	83
10		**1j**		**2j**	3.0	78
11		**1k**		**2k**	3.0	70[c]

[a] Reaction conditions: 1,3-diol (1 mmol), IBX (3.5 mmol).
[b] Isolated yields.
[c] IBX (4.0 mmol) was used.

We have carried out the reaction using fewer equivalents of 2-iodoxybenzoic acid in the case of 2-methyloctane-1,3-diol (**1a**). Thus, treatment of compound **1a** with one equivalent of 2-iodoxybenzoic acid gave a mixture of products **2a**, **3**, and **4** in a ratio of 55:15:30 in 35% yield after recovery of 60% starting diol (**1a**) (Scheme 3).[20] We were surprised to note that there was no hydroxy aldehyde in the mixture of the products formed. The products **2a**, **3**, and **4** were separated and further oxidized individually with one equivalent of 2-iodoxybenzoic acid. Thus, treatment of compound **3** with one equivalent of 2-iodoxybenzoic acid gave α-formyl ketone **4** together with diketone

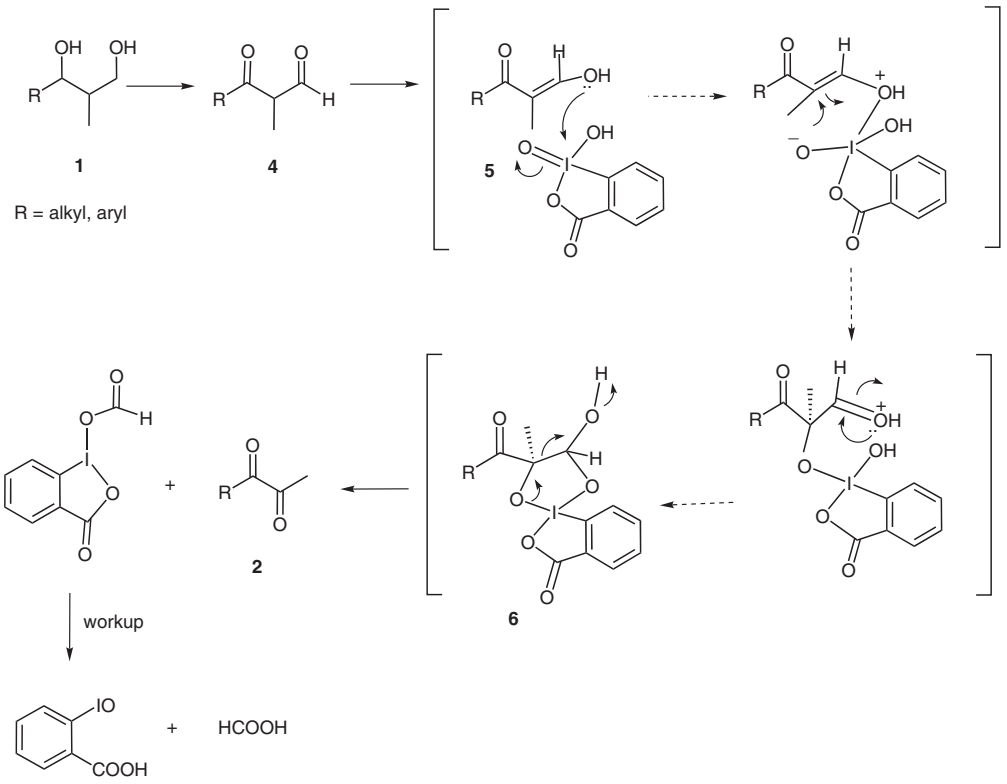


Scheme 3

2a. Further oxidation of α-formyl ketone **4** with one equivalent of 2-iodoxybenzoic acid resulted in a single product, the diketone **2a**. This experiment clearly shows that three equivalents of 2-iodoxybenzoic acid exclusively oxidize the 1,3-diol system to give a 1,2-diketone.

A plausible mechanism is shown in Scheme 4. The α-formyl ketone **4** tautomerizes to form the keto–enol intermediate **5**, which forms a spirocyclic intermediate **6** with 2-iodoxybenzoic acid most likely through nucleophilic attack; simultaneous ring cleavage gives the 1,2-diketone, and on workup formic acid and 2-iodosobenzoic acid are formed.[21]

In conclusion, we have developed a mild and efficient protocol for the conversion of 1,3-diols into 1,2-diketones using the inexpensive and environmentally benign oxidant 2-iodoxybenzoic acid (IBX). The protocol is useful in obtaining 1,2-diketones in the presence of acid- and base-sensitive protecting groups (Table 1, entries 2–4). In



Scheme 4

addition to its simplicity and efficiency, this method provides high yields of 1,2-diketones with high selectivity.

Melting points were recorded on a Büchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini 200, Avance-300 and Varian-unity 400 spectrometers in $CDCl_3$ using TMS as internal standard. MS were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV and ESI/MS.

1,2-Diketones 2; General Procedure

IBX (3.5 mmol) was dissolved in DMSO (1 mL) and to this a soln of 1,3-diol (1 mmol) in THF (4 mL) was added. The mixture was stirred at r.t. for the indicated time (Table 1). On completion of the reaction (TLC), the mixture was diluted with Et_2O (10 mL), filtered through Celite and washed with sat. aq $NaHCO_3$ soln and brine, and dried (anhyd Na_2SO_4). The organic layer was concentrated in vacuo and the resulting product was directly charged on a small column (silica gel, EtOAc–*n*-hexane) to afford the pure 1,2-diketone.

Spectroscopic data for 1-phenylpropane-1,2-dione (**2e**),[22] 1-(4-chlorophenyl)propane-1,2-dione (**2f**),[22] 1-(4-nitrophenyl)propane-1,2-dione (**2h**),[23]1-(4-methoxyphenyl)propane-1,2-dione (**2j**),[24] and naphthalene-1,2-dione (**2k**)[25] are identical to those reported in the literature.

1-Hydroxy-2-methyloctan-3-one (3)

Liquid.

IR (KBr): 3447, 2923, 1658, 1321, 827 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75–3.56 (m, 2 H), 2.80–2.63 (m, 1 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 1.65–1.48 (m, 2 H), 1.38–1.22 (m, 4 H), 1.11 (d, *J* = 7.4 Hz, 3 H), 0.91 (t, *J* = 6.7 Hz, 3 H).

MS (ESI): *m*/*z* = 181 [M + 23]$^+$, 159 [M + 1]$^+$, 128, 100.

HRMS: *m*/*z* [M$^+$] calcd for $C_9H_{18}O_2$: 158.1306; found: 158.1319.

2-Methyl-3-oxooctanal (4)

Liquid.

IR (KBr): 3326, 2921, 1722, 1656, 1271, 779 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.71 (s, 1 H), 3.44 (q, *J* = 6.7, 13.4 Hz, 1 H), 2.48– 2.30 (m, 2 H), 1.54–1.35 (m, 6 H), 1.13 (d, *J* = 7.4 Hz, 3 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

MS (ESI): *m*/*z* = 157 [M + 1]$^+$, 128.

HRMS: *m*/*z* [M$^+$] calcd for $C_9H_{16}O_2$: 156.1150; found: 156.1158.

Octane-2,3-dione (2a)

Liquid.

IR (KBr): 2915, 1645, 1618, 1325, 1219, 772 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.70 (t, *J* = 7.4 Hz, 2 H), 2.31 (s, 3 H), 1.45–1.22 (m, 6 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$, proton-decoupled): δ = 14.4, 22.7, 24.6, 25.2, 31.4, 35.7, 198.0, 198.6.

MS (ESI): *m*/*z* = 143 [M + 1]$^+$, 130, 101, 98.

(4*R*,5*R*,6*R*)-5-(Benzyloxy)-7-(*tert*-butyldiphenylsiloxy)-4,6-dimethylheptane-2,3-dione (2b)

Liquid.

IR (KBr): 2932, 1712, 1637, 1460, 1427, 1389, 1111, 823, 740, 703, 612 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (t, *J* = 7.3 Hz, 4 H), 7.39–7.30 (m, 5 H), 7.29–7.19 (m, 4 H), 7.10–7.07 (m, 2 H), 4.45–4.30 (ABq, *J* = 3.9, 11.7 Hz, 2 H), 3.80–3.74 (m, 2 H), 3.72–3.61 (m, 2 H), 2.01 (s, 3 H), 1.81–1.68 (m, 1 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 1.06 (s, 9 H), 0.99 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, proton-decoupled): δ = 13.4, 14.2, 19.1, 23.4, 27.1, 38.9, 41.5, 66.5, 73.6, 85.2, 127.2, 128.3, 129.9, 133.1, 136.2, 138.5, 198.5, 202.1.

MS (ESI): *m*/*z* = 539 [M + 23]$^+$, 472, 407.

Anal. Calcd for $C_{32}H_{40}O_4Si$: C, 74.38; H, 7.80. Found: C, 74.42; H, 7.86.

(4*R*,5*R*,6*R*)-5,7-(Isopropylidenedioxy)-4,6-dimethylheptane-2,3-dione (2c)

Liquid.

IR (KBr): 2928, 1715, 1622, 1472, 1442, 1365, 1109, 714 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.06 (ABq, *J* = 3.8, 10.8 Hz, 1 H), 3.65 (ABq, *J* = 4.5, 12.1 Hz, 1 H), 3.48 (t, *J* = 11.3 Hz, 1 H), 3.38–3.30 (m, 1 H), 2.28 (s, 3 H), 1.90–1.74 (m, 1 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, proton-decoupled): δ = 11.9, 18.9, 24.5, 29.5, 30.7, 41.9, 65.8, 74.1, 98.3, 198.9, 201.2.

MS (ESI): *m*/*z* = 251 [M + 23]$^+$, 186, 130.

(4*R*,5*R*,6*R*)-5,7-Bis(benzyloxy)-4,6-dimethylheptane-2,3-dione (2d)

Liquid.

IR (KBr): 2926, 2855, 1713, 1606, 1497, 1454, 1356, 1092, 739, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.11 (m, 10 H), 4.52–4.34 (m, 4 H), 4.10 (q, *J* = 6.8, 14.4 Hz, 1 H) 3.85–3.75 (m, 1 H), 3.61–3.56 (m, 1 H), 3.53–3.40 (m, 2 H), 2.01 (s, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$, proton-decoupled): δ = 13.6, 14.4, 24.8, 36.8, 40.8, 71.8, 73.1, 73.7, 84.9, 127.4, 127.5, 127.8, 127.9, 128.2, 128.3, 137.8, 138.5, 198.1, 201.8.

MS (ESI): *m*/*z* = 391 [M + 23]$^+$, 343, 277, 261, 145, 91.

HRMS: *m*/*z* [M$^+$] calcd for $C_{23}H_{28}O_4$: 368.1987; found: 368.1996.

1-(3-Phenoxyphenyl)propane-1,2-dione (2g)

Low-melting solid.

IR (KBr): 2931, 1713, 1676, 1580, 1489, 1438, 1231, 1112, 858, 741, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.4 Hz, 1 H), 7.62 (s, 1 H), 7.42 (t, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 8.2 Hz, 2 H), 7.13 (t, *J* = 7.4 Hz, 2 H), 7.00 (d, *J* = 7.4 Hz, 2 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, proton-decoupled): δ = 26.4, 117.5, 119.8, 121.2, 123.5, 125.2, 131.0, 133.1, 156.7, 158.5, 190.3, 201.5.

MS (EI): *m*/*z* = 241 [M]$^+$, 209, 198, 170, 142, 116, 78, 53.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.97; H, 5.06.

1-(4-Fluorophenyl)propane-1,2-dione (2i)

Low-melting solid.

IR (KBr): 3067, 2350, 1713, 1676, 1581, 1484, 1353, 1285, 1133, 864, 755, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (t, *J* = 7.4 Hz, 2 H), 7.14 (t, *J* = 8.2 Hz, 2 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, proton-decoupled): δ = 25.9, 116.5, 129.9, 133.2, 166.3, 190.4, 199.3.

MS (ESI): *m*/*z* = 166 [M]$^+$, 131, 102.

Anal. Calcd for $C_9H_7FO_2$: C, 65.06; H, 4.25. Found: C, 65.08; H, 4.26%.

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References and Notes

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