An Efficient Method for the α-Acetoxylation of Ketones

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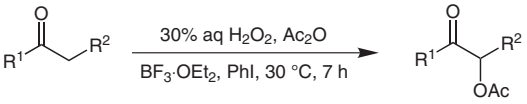
Abstract: α-Acetoxylation of ketones catalyzed by iodobenzene using 30% aqueous hydrogen peroxide and acetic anhydride as the oxidant is an effective and economical method for the preparation of α-acetoxy ketones. The reaction gave the products in good yields without the addition of acetic acid and water.

Key words: acetoxylation, iodobenzene, α-acetoxy ketones, iodine(III) catalysts, oxidation

Previous methods for the preparation of α-acetoxy ketones include the acetolysis of both α-diazo ketones[1] and α-bromo ketones,[2] the treatment of ketones with lead tetraacetate in refluxing benzene,[3] and lead tetraacetate oxidation of trimethylsilyl enol ethers.[4] With the development of hypervalent iodine chemistry, (diacetoxyiodo)benzene was used instead of lead tetraacetate in acetic acid/acetic anhydride in the presence of sulfuric acid to give α-acetoxy ketones.[5] However, stoichiometric amounts of (diacetoxyiodo)benzene are required and equimolecular amounts of iodobenzene are produced as a waste in the reaction. To overcome these drawbacks, polymer-supported, highly recyclable hypervalent iodine(III) reagents have been developed.[6] Recently, Ochiai and co-workers have developed a method for the α-acetoxylation of ketones using only a catalytic amount of iodobenzene.[7] Such a catalytic cycle has not previously been realized, except for electrochemical oxidants.[8]

In the report by Ochiai and co-workers,[7] 3-chloroperoxybenzoic acid serves as a terminal oxidant in the reaction. Amounts of acetic acid and five equivalents of water were also used. It occurred to us that if 30% aqueous hydrogen peroxide and acetic anhydride are used as the oxidant instead of 3-chloroperoxybenzoic acid, then it is not necessary to add acetic acid and water to the reaction (Scheme 1). As expected, exposure of acetophenone to 30% aqueous hydrogen peroxide and acetic anhydride in the presence of a catalytic amount of iodobenzene (20 mol%) and boron trifluoride–diethyl ether (3 equiv) at 30 °C for seven hours afforded 2-acetoxyacetophenone in 79% yield (Table 1, entry 5).

The effect of temperature on the reaction was studied. When the reaction temperature exceeded 35 °C, an unidentified byproduct was generated. As shown in Table 1, raising the temperature to 50 °C resulted in a decrease in the yield to 58% (entry 3). No desired product was formed when the reaction was performed at 80 °C (entry 4). According to the results in Table 2, when the 4′-substituent in acetophenone was an electron-withdrawing group, a higher yield was obtained than when it was an electron-donating group (Table 2, entries 8, 9, 10, 11). When boron trifluoride–acetonitrile was used instead of boron trifluoride–diethyl ether, or additional water (5 equiv) was added to the reaction system, then there was a decrease in the yield (Table 1, entries 6, 7).



Scheme 1

In conclusion, we have reported an effective and economical method for the α-acetoxylation of ketones using 30% aqueous hydrogen peroxide and acetic anhydride as a terminal oxidant. The reaction can be carried out without additional acetic acid and water. Our method is three-to-six times faster (7 h compared to 24–48 h) and has a higher yield compared to the method of Ochiai and co-workers.

Table 1 Effect of Temperature on the α-Acetoxylation of Acetophenone[a]

Entry	Temperature (°C)	Yield[b] (%)
1	20	39
2	30	65
3	50	58
4	80	0
5[c]	30	79
6[d]	30	29
7[e]	30	54

[a] Reaction conditions: acetophenone (0.42 mmol), 30% aq H_2O_2 (1.6 mmol), Ac_2O (8.0 mmol), PhI (0.2 equiv), $BF_3{\cdot}OEt_2$ (3 equiv) for 4 h.
[b] Isolated yields.
[c] Reaction time was 7 h.
[d] $BF_3{\cdot}MeCN$ was used instead of $BF_3{\cdot}OEt_2$.
[e] H_2O (5 equiv) was added.

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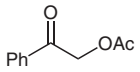
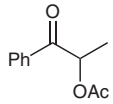
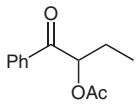
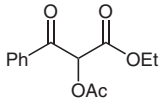
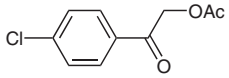
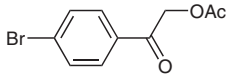
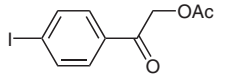
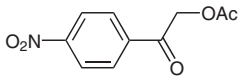
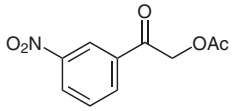
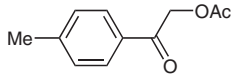
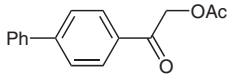
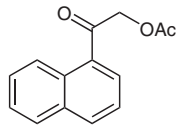
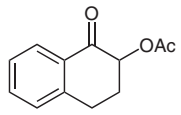
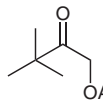
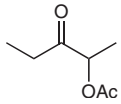
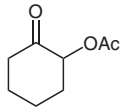
Table 2 α-Acetoxylation of Ketones with 30% Aqueous Hydrogen Peroxide and Acetic Anhydride[a]

Entry	Product	Yield[b] (%)
1		79
2		76
3		74
4		86
5		85
6		75
7		71
8		77
9		76
10		50
11		45
12		40
13		35
14		77
15		73
16		32

[a] Reaction conditions: ketone (0.42 mmol), 30% aq H_2O_2 (1.6 mmol), Ac_2O (8.0 mmol), PhI (0.2 equiv), $BF_3{\cdot}OEt_2$ (3 equiv), 30 °C, 7 h.
[b] Isolated yields.

NMR spectra were performed on a Mercury 4N-PEG-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) spectrometer, using $CDCl_3$ as a solvent and TMS as the internal standard. IR spectra recorded on Nicolet Nexus 670 FT TR spectrophotometer as KBr pellets or KBr film. MS spectra were recorded by the EI method on a HP 5998 mass spectrometer. Elemental analysis was performed by Elementar vario EL analyzer. Melting points are uncorrected.

2-Acetoxyacetophenone; Typical Procedure

A stirred soln of 30% H_2O_2 (0.18 g) and Ac_2O (0.82 g) was cooled to 0 °C.[9] $BF_3{\cdot}OEt_2$ (178 mg, 1.26 mmol) was added slowly to the soln, and then acetophenone (50.4 mg, 0.42 mmol) and iodobenzene (17.2 mg, 0.084 mmol) were added at r.t. The resulting soln was stirred at 30 °C for 7 h (the progress of the reaction was monitored by TLC). Then H_2O (2.5 mL) and Et_2O (15 mL) were added. The mixture was neutralized with a cooled 10% aq Na_2CO_3 soln and extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine, dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 200–300 mesh, petroleum ether–EtOAc, 8:1) to give 2-acetoxyacetophenone; yield: 59 mg (79%).

2-Acetoxyacetophenone

White solid; mp 40–41 °C.

IR (KBr): 1751, 1701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.1 Hz, 2 H), 7.60 (t, *J* = 6.9 Hz, 1 H), 7.47 (dd, *J* = 8.1, 6.9 Hz, 2 H), 5.35 (s, 2 H), 2.23 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.08, 170.37, 134.06, 133.84, 128.79, 127.68, 65.96, 20.52.

MS (EI): *m*/*z* = 178 [M$^+$], 105, 77.

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.68; H, 5.17.

2-Acetoxypropiophenone

Colorless oil.

IR (neat): 1742, 1700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.7 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.47 (dd, *J* = 8.7, 7.2 Hz, 2 H), 5.97 (q, *J* = 6.9 Hz, 1 H), 2.15 (s, 3 H), 1.53 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.80, 170.33, 134.30, 133.51, 128.71, 128.38, 71.35, 20.66, 17.08.

MS (EI): *m*/*z* = 192 [M$^+$], 149, 132, 105, 77.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.01; H, 6.08.

2-Acetoxy-1-phenylbutan-1-one

Colorless oil.

IR (neat): 1740, 1698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.5 Hz, 2 H), 7.54 (t, *J* = 6.9 Hz, 1 H), 7.44 (dd, *J* = 7.5, 6.9 Hz, 2 H), 5.81 (t, *J* = 6.6 Hz, 1 H), 2.14 (s, 3 H), 1.86 (m, 2 H), 1.02 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.49, 170.59, 134.83, 133.42, 128.68, 128.29, 76.28, 24.69, 20.58, 9.76.

MS (EI): *m*/*z* = 206 [M$^+$], 163, 146, 105, 77.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.97; H, 6.72.

Ethyl 2-Acetoxy-3-oxo-3-phenylpropanoate

Colorless oil.

IR (neat): 1752, 1696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.2 Hz, 2 H), 7.61 (t, *J* = 6.6 Hz, 1 H), 7.50 (dd, *J* = 7.2, 6.6 Hz, 2 H), 6.33 (s, 1 H), 4.25 (q, *J* = 6.3 Hz, 2 H), 2.22 (s, 3 H), 1.21 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.65, 169.52, 165.13, 134.19, 129.17, 128.75, 128.45, 74.46, 62.47, 20.48, 13.86.

MS (EI): *m*/*z* = 250 [M$^+$], 205, 105, 77.

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64; Found: C, 62.51; H, 5.44.

2-Acetoxy-4′-chloroacetophenone
White solid; mp 68 °C (Lit.[5] 73 °C).

IR (KBr): 1745, 1694 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9.0 Hz, 2 H), 7.45 (d, *J* = 9.0 Hz, 2 H), 5.27 (s, 2 H), 2.21 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.05, 170.28, 140.33, 132.47, 129.18, 129.12, 65.79, 20.45.

MS (EI): *m*/*z* = 212 [M$^+$], 141, 139, 113, 111.

Anal. Calcd for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27. Found: C, 56.23; H, 3.87.

2-Acetoxy-4′-bromoacetophenone
White solid; mp 83 °C.

IR (KBr): 1744, 1693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.1 Hz, 2 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 5.29 (s, 2 H), 2.22 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.27, 182.74, 170.38, 132.80, 132.20, 129.20, 65.80, 20.53.

MS (EI): *m*/*z* = 258 [M$^+$], 256, 185, 183, 157, 155, 76, 75.

Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 47.19; H, 3.14.

2-Acetoxy-4′-iodoacetophenone
White solid; mp 113 °C.

IR (KBr): 1744, 1692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.5 Hz, 2 H), 7.62 (d, *J* = 7.5 Hz, 2 H), 5.28 (s, 2 H), 2.23 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.58, 170.29, 138.16, 133.38, 129.00, 101.93, 65.73, 20.49.

MS (EI): *m*/*z* = 304 [M$^+$], 231, 202.

Anal. Calcd for $C_{10}H_9IO_3$: C, 39.50; H, 2.98. Found: C, 40.18; H, 2.62.

2-Acetoxy-4′-nitroacetophenone
Yellow solid; mp 121 °C (Lit.[5] 123.8 °C).

IR (KBr): 1748, 1703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.1 Hz, 2 H), 8.07 (d, *J* = 8.1 Hz, 2 H), 5.32 (s, 2 H), 2.20 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.07, 170.20, 150.64, 138.57, 128.86, 124.01, 66.02, 20.36.

MS (EI): *m*/*z* = 223 [M$^+$], 181, 163, 150, 104, 92, 76.

Anal. Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.85; H, 3.97; N: 6.35.

2-Acetoxy-3′-nitroacetophenone
Yellow oil.

IR (neat): 1746, 1706 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (s, 1 H), 8.47 (d, *J* = 8.1 Hz, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 7.75 (dd, *J* = 8.1, 7.8 Hz, 1 H), 5.37 (s, 2 H), 2.24 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.45, 170.21, 148.37, 135.27, 133.29, 130.20, 128.00, 122.61, 65.90, 20.34.

MS (EI): *m*/*z* = 223 [M$^+$], 181, 163, 150, 104, 92, 76.

Anal. Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.70; H, 3.98; N: 6.43.

2-Acetoxy-4′-methylacetophenone
Light yellow solid; mp 82 °C.

IR (KBr): 1748, 1696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 5.31 (s, 2 H), 2.41 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.69, 170.40, 144.80, 131.68, 129.47, 127.80, 65.90, 21.69, 20.54.

MS (EI): *m*/*z* = 192 [M$^+$], 119, 91, 65.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.31; H, 5.86.

2-Acetoxy-4′-phenylacetophenone
Light yellow solid; mp 109 °C.

IR (KBr): 1750, 1702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 6.6 Hz, 2 H), 7.48 (m, 3 H), 5.37 (s, 2 H), 2.25 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.72, 170.40, 146.56, 139.58, 132.86, 128.97, 128.40, 128.32, 127.43, 127.24, 65.99, 20.55.

MS (EI): *m*/*z* = 254 [M$^+$], 181, 153, 152.

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.86; H, 5.22.

2-Acetoxyacetonaphthone
Red oil.

IR (neat): 1747, 1696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (m, 1 H), 8.01 (m, 1 H), 7.85 (m, 2 H), 7.56 (m, 3 H), 5.31 (s, 2 H), 2.25 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.02, 170.43, 133.87, 133.43, 132.29, 130.14, 128.40, 128.26, 127.38, 126.70, 125.47, 124.15, 67.42, 20.50.

MS (EI): *m*/*z* = 228 [M$^+$], 155, 127.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 74.06; H, 5.03.

2-Acetoxy-3,4-dihydronaphthalen-1(2*H*)-one
Red solid; mp 69–70 °C.

IR (KBr): 1740, 1698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.5 Hz, 1 H), 7.51 (dd, *J* = 7.5, 7.8 Hz, 1 H), 7.33 (dd, *J* = 7.5, 7.8 Hz, 1 H), 7.28 (d, *J* = 7.5 Hz, 1 H), 5.56 (m, 1 H), 3.21 (m, 2 H), 2.39 (m, 2 H), 2.23 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.96, 170.20, 143.03, 133.89, 131.52, 128.61, 127.79, 126.93, 74.55, 29.11, 27.92, 20.84.

MS (EI): *m*/*z* = 204 [M$^+$], 162, 144.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 71.03; H, 5.54.

1-Acetoxy-3,3-dimethylbutan-2-one
Colorless oil.

IR (neat): 1752, 1726 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.87 (s, 2 H), 2.15 (s, 3 H), 1.18 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.98, 170.38, 64.43, 42.78, 26.12, 20.51.

MS (EI): *m*/*z* = 158 [M^+], 101, 85, 73, 57.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.27; H, 8.51.

2-Acetoxypentan-3-one
Colorless oil.

IR (neat): 1735, 1675 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.11 (q, *J* = 7.2 Hz, 1 H), 2.51 (q, *J* = 6.9 Hz, 2 H), 2.14 (s, 3 H), 1.41 (d, 7.2 Hz, 3 H), 1.08 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.33, 170.35, 74.43, 31.34, 20.67, 16.19, 7.10.

MS (EI): *m*/*z* = 144 [M^+], 115, 101, 87.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.92; H, 8.08.

2-Acetoxycyclohexanone
White solid; mp 35–36 °C.

IR (neat): 1749, 1726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.17 (dd, *J* = 6.4, 11.2 Hz, 1 H), 2.52 (m, 1 H), 2.40 (m, 1 H), 2.30 (m, 1 H), 2.16 (s, 3 H), 2.12 (m, 1 H), 1.99 (m, 1 H), 1.77 (m, 2 H), 1.68–1.61 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.66, 170.06, 76.53, 40.66, 33.01, 27.11, 23.72, 20.74.

MS (EI): *m*/*z* = 156 [M^+], 113, 85.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.65; H, 7.63.

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(9) If the mixture was stirred at 40 °C for 4 h, it only needed to be cooled to r.t.