

Oxidation of 2-Alkylcycloalkanones with Iodine–Cerium(IV) Salts in Alcohols†

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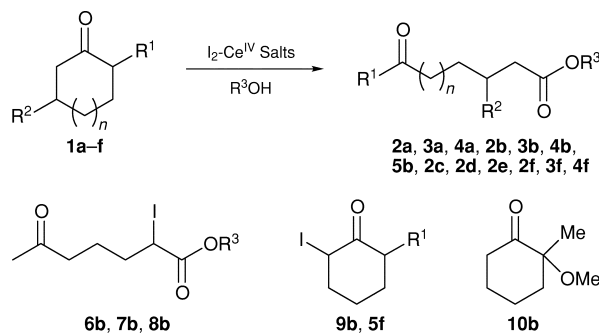
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The reaction of 2-alkylcycloalkanones with iodine–cerium(IV) salts in alcohols (methanol, ethanol, propan-1-ol or propan-2-ol) gave the respective oxo ester in 28–98% yields.

Oxocarboxylic acids and esters are important as intermediates in organic synthesis. There are many syntheses of oxo esters, involving regiospecific oxidative ring-opening of cycloalkanones with ferric salts by oxygen,¹ ring opening oxygenation on treatment with VO(OEt)Cl₂ in alcohols under oxygen,² electrochemical oxidation of enol ethers of cyclohexanone,³ specific cleavage of silyl enol ethers by MoO₂(acac)₂ (Hacac = pentane-2,4-dione) and *tert*-butyl peroxide,⁴ and Mo-catalyzed oxygenation of cyclic ketones by molecular oxygen.⁵ It is known that many of these reactions proceed by a Baeyer–Villiger type process. Atmansani *et al.* have recently reported that the oxidation of 2-methylcyclohexanone by oxygen in the presence of vanadium-containing heteropolyanions in AcOH–H₂O gives 6-oxoheptanoic acid.⁶

We have investigated novel iodination methods using iodine–copper(II) acetate.⁷ These methods, however, have disadvantages in that the iodide ions produced are consumed as copper(I) iodide. During the course of our studies we found new reactions when using iodine–ammonium cerium(IV) nitrate (CAN).⁸

We have also described the reaction of 5 α -cholestan-3-one with iodine and CAN in acetic acid–water (9:1) at 50 °C for 22 h to give 2,3-*seco*-5 α -cholestane-2,3-dioic acid.⁹ Through our studies we have found that iodine–CAN and iodine–cerium(IV) sulfate tetrahydrate (CST)¹⁰ are useful reagents for the syntheses of a large number of iodo compounds. Here we report that the reaction of 2-alkylcycloalkanones **1a–1f** with iodine–cerium(IV) salts in alcohols (methanol, ethanol, propan-1-ol, or propan-2-ol) yields the corresponding oxo ester (Scheme 1). The reaction of 2-methylcyclohexanone **1b** with iodine (0.1 mol. equiv.)–CST (1.5 mol. equiv.) in methanol at 50 °C for 15 h gave methyl 6-oxoheptanoate **2b** (82%). With iodine (0.6 mol. equiv.)–CST (1.0 mol. equiv.), **2b** (29%) and 2-methoxy-2-



- 1a:** $n = 0$, R¹ = CH₃, R² = H
1b: $n = 1$, R¹ = CH₃, R² = H
1c: $n = 1$, R¹ = CH₃, R² = CH₃
1d: $n = 1$, R¹ = Prⁱ, R² = H
1e: $n = 1$, R¹ = Prⁱ, R² = CH₃
1f: $n = 1$, R¹ = Ph, R² = H
2a: $n = 0$, R¹ = CH₃, R² = H, R³ = OMe
2b: $n = 1$, R¹ = CH₃, R² = H, R³ = OMe
2c: $n = 1$, R¹ = CH₃, R² = CH₃, R³ = OMe
2d: $n = 1$, R¹ = Prⁱ, R² = H, R³ = OMe
2e: $n = 1$, R¹ = Prⁱ, R² = CH₃, R³ = OMe
2f: $n = 1$, R¹ = Ph, R² = H, R³ = OMe
3a: $n = 0$, R¹ = CH₃, R² = H, R³ = OEt
3b: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
3c: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
3d: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
3e: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
3f: $n = 1$, R¹ = Ph, R² = H, R³ = OEt
4a: $n = 0$, R¹ = CH₃, R² = H, R³ = OEt
4b: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
4c: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
4d: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
4e: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
4f: $n = 1$, R¹ = Ph, R² = H, R³ = OEt
5a: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
5b: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
5c: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
5d: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
5e: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
5f: $n = 1$, R¹ = Ph, R² = H, R³ = OEt
6b: $n = 1$, R¹ = CH₃, R² = H, R³ = OMe
7b: $n = 1$, R¹ = CH₃, R² = H, R³ = OEt
8b: $n = 1$, R¹ = CH₃, R² = H, R³ = OPrⁿ
9b: $n = 1$, R¹ = CH₃
10b: $n = 1$, R¹ = Ph

Scheme 1

methylcyclohexanone **10b** (59%) were obtained. The results are summarized in Table 1.

As can be seen from Table 1, the reaction provided a general synthesis of oxo ester derivatives. Moreover, it is particularly noteworthy that in contrast to the case of 2-alkylcycloalkanones, the reaction of 2-phenylcyclohexanone yielded oxo esters in high yield. It was found that with 0.6 mol. equiv. of iodine, the 2-methoxy compound was obtained as the major product. In order to clarify the reaction pathway, the reaction of **10b** with iodine–CST was attempted. The reaction of **10b** under the conditions for C–C bond cleavage described above resulted in the recovery

Table 1 Reactions of 2-alkylcycloalkanones with I₂–Ce^{IV} salts in MeOH^a

Reagent (mol. equiv.)	Substrate	T/°C	t/h	Products and yields (%) by NMR ^b (isolated)
CST (1.5)–I ₂ (0.1)	1a	50	7	2a ^{11a} 79 (66)
CAN (1)–I ₂ (0.5)	1b	Room temp.	3.5	2b ^{11a} (28)
CAN (1)–I ₂ (0.1)	1b	50	25	2b (46)
CAS (1)–I ₂ (0.2)	1b	Reflux	10	2b (63)
CST (1)–I ₂ (0.2)	1b	Room temp.	4d	2b (65) (52)
CST (1)–I ₂ (0.6)	1b	50	9	2b (29)
CST (1.5)–I ₂ (0.1)	1b	50	15	2b (82) (71)
CST (1.5)–I ₂ (0.1)	1c	50	10	2c ^{11c} (80) (67)
CST (1.5)–I ₂ (0.1)	1d	50	10	2d ^{11e} (80) (68)
CST (1.5)–I ₂ (0.1)	1e	Reflux	11	2e ^{11f} (72) (60)
CST (1.5)–I ₂ (0.1)	1f	Reflux	10	2f ^{11g} (95) (89)
CAS (1)–I ₂ (0.2)	1f	Reflux	10	2f (81) (67)

^aSubstrate (2.72 mmol) in MeOH (20 ml). ^bYields determined by ¹H NMR with added internal standard methyl benzoate.

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of the starting material. This result eliminates **10b** as an intermediate.

Moreover, we tried the reaction in other alcohols (ethanol, propan-1-ol and propan-2-ol). The results are

Table 2 Reactions of 2-alkylcycloalkanones with I₂-CST in R³OH^a

Substrate	Solvent	T/°C	t/h	Products (%) ^b
1a	EtOH	65	20	3a ^{11b} (61)
1a	Pr ⁿ OH	65	21	4a (63)
1b	EtOH	Room temp.	4d	3b ^{11d} (66) 7b (16)
1b	EtOH	65	20	3b (57)
1b	Pr ⁿ OH	Room temp.	6d	4b (36) 8b (27)
1b	Pr ⁿ OH	65	20	4b (51)
1b	Pr ⁱ OH	Room temp.	6d	5b (43)
1b	Pr ⁱ OH	65	20	5b (44)
1f	EtOH	65	18	3f ^{11h} (90)
1f	Pr ⁿ OH	65	7	4f (98)

^aSubstrate (2.72 mmol) with I₂ (0.54 mmol)-CST (2.72 mmol) in alcohol (20 ml). ^bIsolated yield.

summarized in Table 2. For the more bulky alkoxy groups, the yields of the oxo esters are diminished compared with those for the methoxy reactions. However, in the case of 2-phenylcyclohexanone, the yields were not affected.

In conclusion, the present method provides a new alternative to others previously reported for the preparation of oxo esters from cyclic ketones by using I₂-cerium(IV) salts in alcohol.

Experimental

IR spectra were measured using a Jasco FT-IR 230. NMR spectra were measured on a JEOL GSX 400 spectrometer with the samples dissolved in deuteriochloroform with Me₄Si as the internal standard. High-resolution mass spectra were recorded at 75 eV on a JEOL JMS-O1 SG-2 instrument with a direct inlet.

General Procedure. Reaction of 2-Methylcyclohexanone with CST-I₂ in MeOH.—A mixture of 2-methylcyclohexanone **1b** (0.305 g, 2.72 mmol), iodine (0.138 g, 0.54 mmol) and cerium(IV) sulfate tetrahydrate (1.099 g, 2.72 mmol) in MeOH (20 ml) was stirred at room temperature for 4 days. The white precipitate of Ce^{III} salt was filtered off and the solvent was evaporated under reduced pressure. The residue was poured into water (20 ml) and extracted with dimethyl ether (50 ml). The ethereal solution was washed successively with aq. sodium thiosulfate (10 ml), saturated aq. NaCl (10 ml) and water (10 ml) and dried (Na₂SO₄). Evaporation of the solvent gave a pale yellow oil. Methyl benzoate was added as an internal standard if the yield was to be estimated by ¹H NMR spectroscopy. The oil was chromatographed on silica gel with hexane-ether (4:1) as the eluent to give the corresponding compound **2b** as a pale yellow oil (0.225 g, 52%).

Spectroscopic and Analytical Data.—**4a:** Pale yellow oil, $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1718 and 1172; δ_{H} (CDCl₃) 4.01–4.06 (t, 2 H), 2.50–2.54 (t, 2 H), 2.32–2.36 (t, 2 H), 2.15 (s, 3 H), 1.87–1.91 (m, 2 H), 1.62–1.68 (m, 2 H) and 0.92–0.96 (t, 3 H); δ_{C} (CDCl₃) 208.0, 173.3, 66.0, 42.5, 33.3, 29.9, 22.0, 19.0 and 10.4 (Found: M⁺, 172.1086. C₉H₁₆O₃ requires M_r, 172.1100).

4b: Pale yellow oil, $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1735 and 1716; δ_{H} (CDCl₃) 4.01–4.04 (t, 2 H), 2.45–2.48 (t, 2 H), 2.30–2.34 (t, 2 H), 2.14 (s, 3 H), 1.60–1.68 (m, 6 H), and 0.92–0.96 (t, 3 H); δ_{C} (CDCl₃) 208.5, 173.5, 65.9, 43.3, 34.1, 29.9, 24.5, 23.2, 22.0 and 10.4 (Found: M⁺, 186.1227. C₁₀H₁₈O₃ requires M_r, 186.1256).

5b: Pale yellow oil, $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1727 and 1719; δ_{H} (CDCl₃) 4.97–5.02 (m, 1 H), 2.45–2.48 (t, 2 H), 2.26–2.29 (t, 2 H), 2.14 (s, 3 H), 1.60–1.61 (m, 4 H) and 1.21–1.27 (d, 6 H); δ_{C} (CDCl₃) 208.4, 172.8, 67.5, 43.2, 34.4, 29.8, 24.5, 23.2, 21.8 and 21.8; MS (EI): m/z 186 [M⁺], 127, 58, 43; MS (CI): m/z 187 [M + I]⁺.

6b: $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1740 and 1156; δ_{H} (CDCl₃) 4.48 (t, 1 H), 3.68 (s, 3 H), 2.43 (s, 3 H), 2.36 (t, 2 H), 1.88–2.02 (m, 2 H), 1.72–1.84 (m, 1 H) and 1.54–1.68 (m, 1 H); δ_{C} (CDCl₃) 202.2, 173.3, 51.6, 33.7, 33.0, 32.2, 26.1 and 24.6 (Found: M⁺, 283.9939. C₈H₁₃O₃I requires M_r, 283.9909).

7b: $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1732; δ_{H} (CDCl₃) 4.48 (t, 1 H), 4.13 (q, 1 H), 2.43 (s, 3 H), 2.35 (dt, 2 H), 1.88–2.02 (m, 2 H), 1.72–1.84 (m, 1 H), 1.55–1.68 (m, 1 H) and 1.26 (t, 3 H); δ_{C} (CDCl₃) 202.2, 172.9, 60.5, 33.8, 33.3, 32.4, 26.1, 24.6 and 14.2 (Found: M⁺, 298.0038. C₉H₁₅O₃I requires M_r, 298.0066).

8b: $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1732; δ_{H} (CDCl₃) 4.50 (t, 1 H), 4.04 (t, 2 H), 2.43 (s, 3 H), 2.36 (dt, 2 H), 1.91–2.03 (m, 2 H), 1.71–1.84 (m, 1 H), 1.55–1.71 (m, 1 H) and 0.94 (t, 3 H); δ_{C} (CDCl₃) 202.2, 172.9, 66.1, 33.7, 33.2, 32.3, 26.1, 24.6, 21.9 and 10.4 (Found: M⁺, 312.0209. C₁₀H₁₇O₃I requires M_r, 312.0222).

9b: Colorless plates; mp 63–64°C; $\nu_{\max}/\text{cm}^{-1}$ (KBr) 1716; δ_{H} (CDCl₃) 4.88 (d, 1 H), 2.74 (m, 1 H), 2.60 (m, 1 H), 2.11–2.31 (m,

2 H), 1.74–1.83 (m, 2 H), 1.40–1.54 (m, 1 H) and 1.13 (d, 3 H); δ_{C} (CDCl₃) 203.9, 44.5, 42.3, 37.5, 36.1, 27.9 and 15.9 (Found: M⁺, 237.9831. C₇H₁₁OI requires M_r, 237.9855).

4f: Pale yellow oil; $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1731 and 1685; δ_{H} (CDCl₃) 7.93–7.96 (2 H), 7.52–7.55 (1 H), 7.42–7.47 (2 H), 4.00–4.04 (t, 2 H), 2.97–3.00 (t, 2 H), 2.35–2.38 (t, 2 H), 1.71–1.80 (m, 4 H), 1.61–1.67 (m, 2 H) and 0.91–0.95 (t, 3 H); δ_{C} (CDCl₃) 199.7, 173.5, 136.9, 133.0, 128.6, 128.6, 128.0, 128.0, 65.9, 38.1, 34.1, 24.7, 23.7, 22.0 and 10.4; MS (EI): m/z 248 [M⁺], 189(M⁺ – 59), 105 and 77; MS (CI): m/z 249 [M + I]⁺.

5f: Colorless plates; mp 73–76°C; $\nu_{\max}/\text{cm}^{-1}$ (KBr): 1712; δ_{H} (CDCl₃) 7.33–7.39 (m, 2 H), 7.25–7.31 (m, 1 H), 7.11–7.17 (m, 2 H), 4.78–4.82 (m, 1 H), 4.75 (dd, 1 H) and 1.89–2.32 (m, 6 H); δ_{C} (CDCl₃) 204.6, 137.8, 128.7, 128.4, 127.2, 50.4, 37.0, 34.8, 31.4 and 22.0 (Found: M⁺, 299.9985. C₁₂H₁₃OI requires M_r, 300.0011).

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