Regioselective iodination of hydroxylated aromatic ketones

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Abstract

A variety of *ortho* hydroxy substituted aromatic carbonyl compounds were regioselectively mono or diiodinated with iodine and iodic acid in excellent yields.

Keywords: Benzophenone, butyrophenone, iodination, molecular iodine, iodic acid

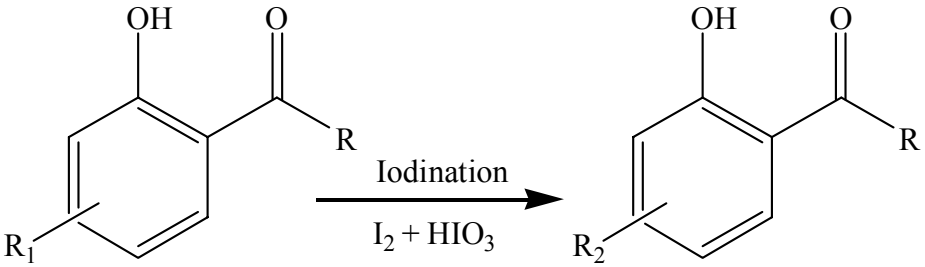
Introduction

Iodohydroxy aromatic ketones can be prepared by Fries rearrangement[1] of iodinated phenyl aromatic esters, however, after the Fries rearrangement, steam distillation is required to separate the isomers which is a time consuming method and iodophenols are not easily available.

In recent years, direct iodination methods have been intensively developed using iodinium donating systems, such as iodine nitrogen dioxide,[2] iodine-F-TEDA-[1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane-bis-(tetrafluoroborate)],[3] bis-*N*-iodosuccinimide,[4] iodine-di-iodine pentoxide,[5] mercury(II)-oxide-iodine,[6] iodine monochloride,[7] bis(pyridine)iodonium(I) tetrafluoroborate CF_3SO_3H,[8] NIS-CF_3SO_3H,[9] iodine silver sulfate,[10] iodine-mercury salts,[11] NaOCl-NaI,[12] iodine/$Na_2S_2O_8$[13] and iodine-$(NH_4)_2$ S_2O_8-$CuCl_2$-Ag_2SO_4.[14] Iodination of resorcinol derivatives and hydroxy chromones has been carried out using iodine and sodium hydroxide,[15] potassium iodide and potassium iodate[16] in acetic acid medium. However, most of these methods involve hazardous or toxic reagents.

Result and Discussion

We here report a practical and regioselective aromatic iodination. A combination of iodine and iodic acid has been found to be an excellent reagent for the efficient iodination of aromatic carbonyl compounds such as hydroxy butyrophenones and hydroxy benzophenones. These reactions are carried out at 35-40 ˚C using commercial 95% aqueous ethyl alcohol as a solvent.
A variety of *ortho* hydroxy substituted aromatic carbonyl compounds were selected for the iodination reaction using iodine and iodic acid. The iodination occurs regioselectively and the C-iodination took place at *ortho* or/and *para* positions. When the *o*-position was blocked with a substituent, then iodination took place at *p*-position and vice versa. The diiodination occurs if ortho and para positions are unsubstituted. Iodination does not occur in the side chain i.e. -CO-CH_2-R or -CH_3; only nuclear iodination takes place. The iodination procedure is very simple; chemicals are not hazardous and can be weighed easily.



1a-j **2a-j**

R = CH_2-CH_2-CH_3

R_1 = 1a, 4-CH_3	**R_2** = 2a, 3,5-I, 4-CH_3
1b, 5-Cl	2b, 3-I, 5-Cl
1c, 5-Br	2c, 3-I, 5-Br
1d, 3-CH_3	2d, 3-CH_3, 5-I
1e, 4,6-CH_3	2e, 3,5-I, 4,6-CH_3

R = C_6H_5

R_1 = 1f, 5-CH_3	**R_2** = 2f, 3-I, 5-CH_3
1g, 4-CH_3	2g, 3,5-I, 4-CH_3
1h, 5-Cl	2h, 3-I, 5-Cl
1i, 3-Cl	2i, 3-Cl, 5-I
1j, 4,6-CH_3	2j, 3,5-I, 4,6-CH_3

Scheme 1

Experimental Section

General Procedures. Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds has been checked by TLC. The IR spectra were recorded on FTIR Perkin-Elmer Spectrometer; ^{1}H NMR spectra were recorded on Gemini 300 MHz in $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra are recorded on VG 7070H mass spectrometer.

General procedure for iodination of hydroxy aromatic ketones by iodine and iodic acid (2a-2j). To a mixture of 2-hydroxy aryl ketones (0.05 mol) and iodine (0.02 mol) dissolved in ethanol (30 mL), iodic acid (0.01 mol) dissolved in water (1 mL) was added while stirring for 10 min. The reaction mixture was then stirred for 1.5 h at 35-40 ^{0}C. The solid product separates out on dilution with water (15-20mL). It was filtered, washed with saturated sodium thiosulphate solution to remove the excess of iodine, washed with cold water and crystallized from ethyl alcohol.

1-(2-Hydroxy-3, 5-diiodo-4-methyl-phenyl) butan-1-one (2a). Yield 81%, mp 98 °C; IR (cm^{-1}) 1633 (C=O), 1470 (C=C), 1162 (C-O). ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, 3H, CH_2-CH_2-C*H*$_3$), 1.72 (m, 2H, CH_2-C*H*$_2$-CH_3), 2.86 (t, 2H, C*H*$_2$-CH_2-CH_3), 2.35 (s, 3H, 4Ar-CH_3), 8.10 (s, 1H, 6Ar-H); ^{13}C NMR δ 15.7, 19.8, 21.4, 47.7, 89.3, 96.8, 124.1, 133.5, 159.7, 166.9, 198.6. M/z (relative intensity): M^+ 430 (20), 261 (100), 105 (22), 77 (24), 51 (12). Anal. calcd for $C_{11}H_{12}I_2O_2$: C, 30.72; H, 2.81; I, 59.02. Found: C, 30.67; H, 2.77; I, 59.10.

1-(2-Hydroxy-3-iodo-5-chloro-phenyl) butan-1-one (2b). Yield 76 %, mp 163 °C; IR (cm-^{1}) 1640 (C=O), 1449 (C=C), 1163 (C-O). ^{1}H NMR ($CDCl_3$) δ: 0.96 (t, 3H, CH_2-CH_2-C*H*$_3$), 1.74 (m, 2H, CH_2-C*H*$_2$-CH_3), 2.86 (t, 2H, C*H*$_2$-CH_2-CH_3), 7.75 (s, 1H, 6Ar-H), 8.13 (s, 1H, 4Ar-H). M/z (Relative intensity): M^+ 324 (38), 281 (100), 126 (21), 91 (17), 63 (10). Anal. calcd for $C_{10}H_{10}ClIO_2$: C, 37.01; H, 3.11; I, 39.10. Found: C, 37.06; H, 3.07; I, 39.18.

1-(2-Hydroxy-3-iodo-5-bromo-phenyl) butan-1-one (2c). Yield 78%, mp 127 °C; IR (cm-^{1}) 1629 (C=O), 1565 (C=C), 1151 (C-O). ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, 3H, CH_2-CH_2-C*H*$_3$), 1.72 (m, 2H, CH_2-C*H*$_2$-CH_3), 2.85 (t, 2H, C*H*$_2$-CH_2-CH_3), 7.8 (s, 1H, 6Ar-H), 8.15 (s, 1H, 4Ar-H). M/z (Relative intensity): M^+ 368 (32), 325 (100), 170 (28), 91 (13), 63 (08). Anal. calcd for $C_{10}H_{10}BrIO_2$: C, 32.55; H, 2.73; I, 34.39. Found: C, 32.64; H, 2.83; I, 34.46.

1-(2-Hydroxy-3-methyl-5-iodo-phenyl) butan-1-one (2d). Yield 80%, mp 119 °C; IR (cm-^{1}) 1637 (C=O), 1580 (C=C), 1158 (C-O). ^{1}H NMR ($CDCl_3$) δ: 0.98 (t, 3H, CH_2-CH_2-C*H*$_3$), 1.71 (m, 2H, CH_2-C*H*$_2$-CH_3), 2.85 (t, 2H, C*H*$_2$-CH_2-CH_3), 2.33 (s, 3H, 3Ar-CH_3), 7.78 (s, 1H, 4Ar-H), 8.15 (s, 1H, 6Ar-H). M/z (Relative intensity): M^+ 304 (32), 261 (100), 106 (14), 77 (21), 51 (10). Anal. calcd for $C_{11}H_{13}IO_2$: C, 43.44; H, 4.31; I, 41.73. Found: C, 43.57; H, 4.25; I, 41.70.

1-(2-Hydroxy-3, 5-diiodo-4, 6-dimethyl-phenyl) butan-1-one (2e). Yield 75%, mp 181°C; IR (cm^{-1}): 1649 (C=O), 1585 (C=C), 1158 (C-O). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H, CH_2-CH_2-C*H*$_3$), 1.77 (m, 2H, CH_2-C*H*$_2$-CH_3), 2.85 (t, 2H, C*H*$_2$-CH_2-CH_3), 2.35 (s, 3H, 4Ar-CH_3), 2.35 (s, 3H,

6Ar-CH_3). M/z (Relative intensity): M^+ 444 (40), 401 (100), 126 (25), 104 (18), 77 (23), 51 (08). Anal. calcd for $C_{12}H_{14}I_2O_2$: C, 32.46; H, 3.18; I, 57.16. Found: C, 32.42; H, 3.21; I, 57.11.

(2-Hydroxy-3-iodo-5-methyl phenyl) phenyl methanone (2f). Yield 82%, mp 80°C; IR (cm^{-1}): 1627 (C=O), 1598 (C=C), 1188 (C-O). ^1H NMR ($CDCl_3$) δ: 2.23 (s, 3H, Ar-CH_3), 7.75-7.83 (m, 7H, Ar-H); ^{13}C NMR δ 20.8, 87.4, 127.3, 129.2, 129.9, 130.2, 130.6, 131.3, 131.8, 133.7, 138.9, 144.7, 167.8, 190.2. M/z (Relative intensity): M^+ 337 (38), 261 (100), 105 (58),77 (20), 51 (52). Anal. calcd for $C_{14}H_{11}IO_2$: C, 49.73; H, 3.28; I, 37.53. Found: C, 49.77; H, 3.31; I, 37.59.

(2-Hydroxy-3,5-diiodo-4-methyl phenyl) phenyl methanone (2g). Yield 84%, mp 121°C; IR (cm^{-1}): 1626 (C=O), 1575 (C=C), 1188 (C-O). ^1H NMR ($CDCl_3$) δ: 2.23 (s, 3H, Ar-CH_3), 7.25-8.03 (m, 6H, Ar-H). M/z (Relative intensity): M^+ 464 (63), 338 (100), 261 (37),105 (66), 77 (64), 51 (20). Anal. calcd for $C_{14}H_{10}I_2O_2$: C, 36.24; H, 2.17; I, 54.70. Found: C, 36.25; H, 2.21; I, 54.74.

(2-Hydroxy-3-iodo-5-chloro phenyl) phenyl methanone (2h). Yield 80%, mp 118 °C; IR (cm^{-1}): 1667 (C=O), 1549 (C=C), 1183 (C-O). ^1H NMR ($CDCl_3$) δ: 7.72-7.83 (m, 7H, Ar-H). M/z (Relative intensity): M^+ 358 (68), 281 (100), 105 (67), 77 (62), 51 (24). Anal. calcd for $C_{13}H_8ClIO_2$: C, 43.55; H, 2.25; I, 35.39. Found: C, 43.61; H, 2.27; I, 35.42.

(2-Hydroxy-3-chloro-5-iodo phenyl) phenyl methanone (2i). Yield 82%, mp 172 °C; IR (cm^{-1}): 1644 (C=O), 1579 (C=C), 1131 (C-O). ^1H NMR ($CDCl_3$) δ: 7.47-7.82 (m, 7H, Ar-H). M/z (Relative intensity): M^+ 358 (24), 281 (100), 105 (64), 77 (62), 51 (18). Anal. calcd for $C_{13}H_8ClIO_2$: C, 43.55; H, 2.25; I, 35.39. Found: C, 43.64; H, 2.24; I, 35.44.

(2-Hydroxy-3,5-diiodo-4,6-dimethyl phenyl) phenyl methanone (2j). Yield 75%, mp 133 °C; IR (cm^{-1}): 1625 (C=O), 1592 (C=C), 1188 (C-O). ^1H NMR ($CDCl_3$) δ: 2.23 (s, 3H, Ar-CH_3), 2.24 (s, 3H, Ar-CH_3), 7.21-7.86 (m, 5H, Ar-H). M/z (Relative intensity): M^+ 478 (64), 401 (100), 121 (72), 106 (64),77 (50), 51 (20). Anal. calcd for $C_{15}H_{12}I_2O_2$: C, 37.69; H, 2.53; I, 53.09. Found: C, 37.65; H, 2.58; I, 53.05.

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