

Regioselective iodination of hydroxylated aromatic ketones

Bhagwan R. Patil^a, Sudhakar R. Bhusare^{c*}, Rajendra P. Pawar^a,
and Yeshwant B. Vibhute^{b*}

^aOrganic Chemistry Synthesis Lab. Dnyanopasak College, Parbhani-431401, India.

^bP. G. Department of Chemistry, Yeshwant Mahavidyalaya, Nanded-431 602, India.

^cDepartment of Chemistry, Shri Shivaji College, Parbhani-431401, India.

E-mail: bhusare71@yahoo.com

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

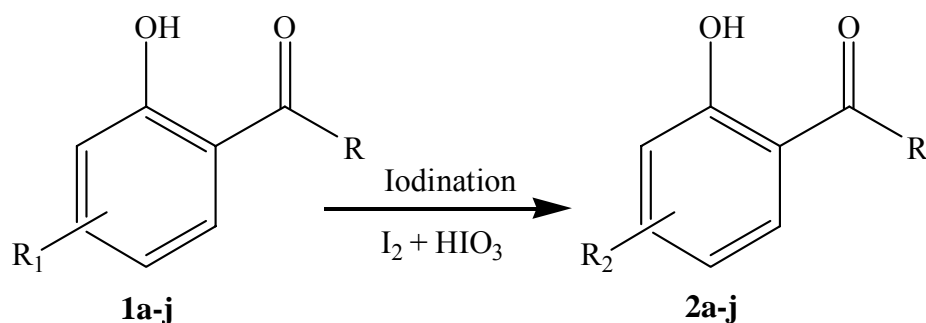
Iodoxy aromatic ketones can be prepared by Fries rearrangement¹ of iodinated phenyl aromatic esters, however, after the Fries rearrangement, steam distillation is required to separate the isomers which is a time consuming method and iodophenols are not easily available.

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 CF₃SO₃H,⁸ NIS-CF₃SO₃H,⁹ iodine silver sulfate,¹⁰ iodine-mercury salts,¹¹ NaOCl-NaI,¹² iodine/Na₂S₂O₈¹³ and iodine-(NH₄)₂ S₂O₈-CuCl₂-Ag₂SO₄.¹⁴ Iodination of resorcinol derivatives and hydroxy chromones has been carried out using iodine and sodium hydroxide,¹⁵ potassium iodide and potassium iodate¹⁶ 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-CH₂-R or -CH₃; only nuclear iodination takes place. The iodination procedure is very simple; chemicals are not hazardous and can be weighed easily.



R = CH₂-CH₂-CH₃

R₁ = 1a, 4-CH₃

1b, 5-Cl

1c, 5-Br

1d, 3-CH₃

1e, 4,6-CH₃

R₂ = 2a, 3,5-I, 4-CH₃

2b, 3-I, 5-Cl

2c, 3-I, 5-Br

2d, 3-CH₃, 5-I

2e, 3,5-I, 4,6-CH₃

R = C₆H₅

R₁ = 1f, 5-CH₃

1g, 4-CH₃

1h, 5-Cl

1i, 3-Cl

1j, 4,6-CH₃

R₂ = 2f, 3-I, 5-CH₃

2g, 3,5-I, 4-CH₃

2h, 3-I, 5-Cl

2i, 3-Cl, 5-I

2j, 3,5-I, 4,6-CH₃

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; ^1H 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 $^\circ\text{C}$. 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 $^\circ\text{C}$; IR (cm^{-1}) 1633 (C=O), 1470 (C=C), 1162 (C-O). ^1H NMR (CDCl_3) δ : 0.97 (t, 3H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.72 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 2.86 (t, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 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 $\text{C}_{11}\text{H}_{12}\text{I}_2\text{O}_2$: 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 $^\circ\text{C}$; IR (cm^{-1}) 1640 (C=O), 1449 (C=C), 1163 (C-O). ^1H NMR (CDCl_3) δ : 0.96 (t, 3H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.74 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 2.86 (t, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 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 $\text{C}_{10}\text{H}_{10}\text{ClIO}_2$: 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 $^\circ\text{C}$; IR (cm^{-1}) 1629 (C=O), 1565 (C=C), 1151 (C-O). ^1H NMR (CDCl_3) δ : 0.97 (t, 3H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.72 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 2.85 (t, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 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 $\text{C}_{10}\text{H}_{10}\text{BrIO}_2$: 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 $^\circ\text{C}$; IR (cm^{-1}) 1637 (C=O), 1580 (C=C), 1158 (C-O). ^1H NMR (CDCl_3) δ : 0.98 (t, 3H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.71 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 2.85 (t, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 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 $\text{C}_{11}\text{H}_{13}\text{IO}_2$: 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 $^\circ\text{C}$; IR (cm^{-1}): 1649 (C=O), 1585 (C=C), 1158 (C-O). ^1H NMR (CDCl_3): δ 0.97 (t, 3H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.77 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 2.85 (t, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 2.35 (s, 3H, 4Ar- CH_3), 2.35 (s, 3H,

6Ar-CH₃). M/z (Relative intensity): M⁺ 444 (40), 401 (100), 126 (25), 104 (18), 77 (23), 51 (08). Anal. calcd for C₁₂H₁₄I₂O₂: 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 (CDCl₃) δ: 2.23 (s, 3H, Ar-CH₃), 7.75-7.83 (m, 7H, Ar-H); ¹³C 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 C₁₄H₁₁IO₂: 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 (CDCl₃) δ: 2.23 (s, 3H, Ar-CH₃), 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 C₁₄H₁₀I₂O₂: 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 (CDCl₃) 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 C₁₃H₈ClIO₂: 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 (CDCl₃) 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 C₁₃H₈ClIO₂: 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 (CDCl₃) δ: 2.23 (s, 3H, Ar-CH₃), 2.24 (s, 3H, Ar-CH₃), 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 C₁₅H₁₂I₂O₂: C, 37.69; H, 2.53; I, 53.09. Found: C, 37.65; H, 2.58; I, 53.05.

Acknowledgements

The authors are thankful to the Principal, Yeshwant Mahavidyalaya, Nanded and Principal, Dnyanopasak Mahavidyalaya, Parbhani for providing laboratory facilities and Director of ICT Hyderabad for providing spectra's of samples. Authors are also thankful to UGC, New Delhi for sanctioning major research grant.

References

1. Blatt, A. H. *Org. React.* **1942**, *1*, 342.
2. Noda, Y.; Kashima, M. *Tetrahedron Lett.* **1997**, *38*, 6225.
3. Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305.
4. Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081.
5. Brazdil, I. C.; Cuter, C. J. *J. Org. Chem.* **1996**, *61*, 9621.
6. Orito, K.; Hatakeyama, T.; Takeo, M.; Sugimoto, H.; *Synthesis* **1995**, 1273.
7. Hubig, S. M.; Jung, W.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 6233.
8. Barluenga, J.; Gonzalez, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asensia, G. *J. Org. Chem.* **1993**, *58*, 2058.
9. Olah, G. A.; Wang, D.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, *58*, 3194.
10. Sy, W. W. *Tetrahedron Lett.* **1993**, *34*, 6223.
11. Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1994**, *50*, 5139.
12. Edgar, K. J.; Falling, S. N., *J. Org. Chem.*, **1990**, *55*, 5287.
13. Elbs, K.; Jaroslawzee, A. *J. Prakt. Chem.*, **1913**, *88*, 92.
14. Marko, D. M.; Belyoew. U. A. *Khim, Referat, Zhur.* **1941**, *4*, 49.
15. Hisao, *J. Pharm. Soc. Jpn.* **1943**, *13*, 63. (Chem. Abstr. **1950**, *44*, 72650)
16. Segalle, *Monatsh. Chem.*, **1896**, *17*, 314.