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### An efficient iodination of hydroxylated aromatic ketones by using iodine and iodic acid

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#### Abstract

*A simple and efficient method for iodination of new substituted  $\alpha$ -Chloro-hydroxyacetophenones and substituted hydroxypropiophenones in excellent yields using iodine and iodic acid.*

**Key words:** Iodination, Substituted  $\alpha$ -Chloro-hydroxyacetophenones, substituted hydroxypropiophenones, molecular iodine, iodic acid.

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#### INTRODUCTION

Iodoaromatic compounds have importance in medicinal and pharmaceutical research [1,2]. Aromatic iodides have long been used in organic synthesis as versatile intermediates that can be transformed into a variety of functional groups [3]. They can be easily functionalized through metal-catalyzed cross coupling reactions [4] in the synthesis of many interesting natural products [5] and bioactive materials [6].

Iodohydroxy aromatic ketones can be prepared by Fries rearrangement [7] of iodinated phenyl aromatic esters; however, after the Fries rearrangement, steam distillation is required to separate the isomer which is a time consuming method and iodophenols are not easily available.

Recently direct iodination methods have been intensively developed using iodonium donating system, such as iodine-nitrogen dioxide [8], iodine F-TEDA-[1-chloromethyl-4-fluoro-1, 4-diazoniabicyclo [2,2,2] octane-bis-(tetrafluoroborate)] [9], bis-N-iodosuccinimide [10], trichloroisocyanuric acid/I<sub>2</sub>/Wet SiO<sub>2</sub> [11], mercury(II)-oxide-iodine [12], iodinemonochloride [13], bis(pyridine)iodonium(I), tetrafluoroborate CF<sub>3</sub>SO<sub>3</sub>H [14], NIS-CF<sub>3</sub>SO<sub>3</sub>H [15], iodine silver sulfate [16], iodine-mercury salts [17], NaOCl-NaI [18] and N-chlorosuccinimide and NaI [19]. However most of these methods has hazardous or toxic, costly reagents, high reaction temperature conditions and for long reaction time.

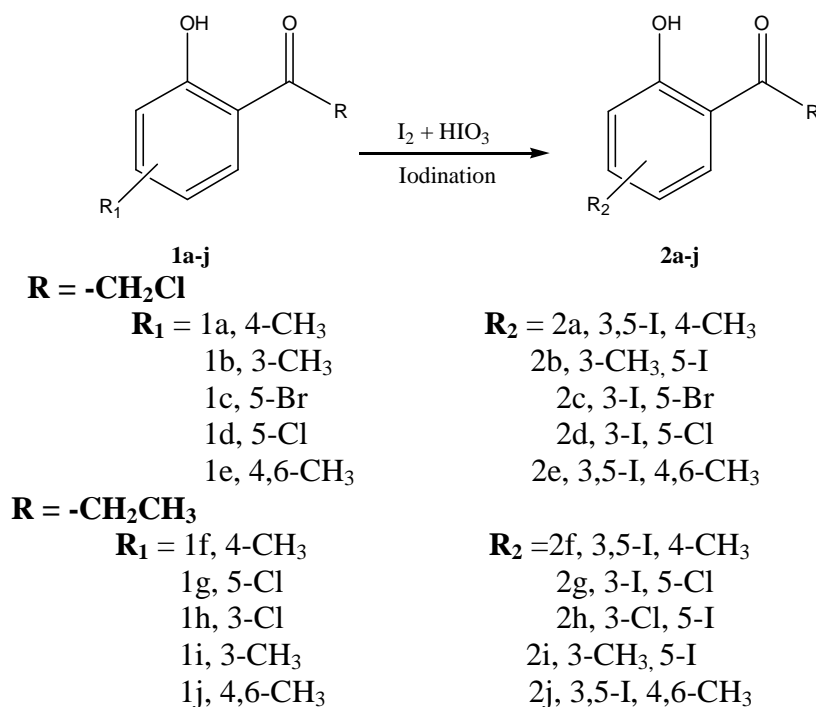
## MATERIALS AND METHODS

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a FTIR Perkin-Elmer spectrometer. <sup>1</sup>H NMR spectra were recorded on a Gemini 300-MHz instrument in CDCl<sub>3</sub> as solvent and TMS as an internal standard. The mass spectra were recorded on a Jeol D-300 spectrometer at 70 eV. Elemental analysis was carried out on a Carlo Erba 1108 analyzer. The halogen analysis was carried out in laboratory by the Parr bomb method. The purity of products was checked by thin-layer chromatography (TLC) on silica-gel.

### General procedures for iodination of hydroxy aromatic ketones (2a-j):

To a mixture of 2-hydroxy aryl ketones (50 mmole) and iodine (20 mmole) dissolved in ethyl alcohol (25 ml), iodic acid (10 mmole) 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<sup>o</sup>C. The solid products separate out on dilution with water (15-20 ml). It was filtered, washed with saturated sodium thiosulphate solution to remove the excess of iodine, washed with water and crystallized from ethyl alcohol.

### Scheme-1 Iodination of hydroxylated ketones by using iodine and iodic acid



**2-Chloro-1-(2-hydroxy-3,5-diiodo-4-methyl-phenyl)-ethanone (2a):** Yield 76 %, m.p.151<sup>o</sup>C; **IR (KBr):** 1656 (>C=O), 1595 (>C=C<), 1172 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ2.32 (s, 3H, Ar-CH<sub>3</sub>), δ4.94 (s, 2H, -CH<sub>2</sub>Cl), δ8.14 (s, 1H, 6Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 436.5 (54), 387 (100), 261(78), 105(16), 77(14), 51(18). Anal. Calcd. For C<sub>9</sub>H<sub>7</sub>O<sub>2</sub>I<sub>2</sub>Cl : C, 24.74; H, 1.60; X, 66.32 %. Found: C, 24.62; H, 1.51; X, 66.20 %.

**2-Chloro-1-(2-hydroxy-5-iodo-3-methyl-phenyl)-ethanone (2b):** Yield 81 %, m.p.80<sup>o</sup>C; **IR (KBr):** 1653 (>C=O), 1615 (>C=C<), 1165 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ2.27 (s, 3H, Ar-CH<sub>3</sub>), δ4.90 (s, 2H, -CH<sub>2</sub>Cl), δ7.88 (s, 1H, 6Ar-H), δ7.98 (s, 1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 310.5 (51), 261 (100), 106(69), 77(24), 51(20). Anal. Calcd. For C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>ICl : C, 34.78; H, 2.57; X, 52.33 %. Found: C, 34.67; H, 2.48; X, 52.24 %.

**2-Chloro-1-(5-bromo-2-hydroxy-3-iodo-phenyl)-ethanone (2c):** Yield 73 %, m.p.105<sup>0</sup>C; **IR (KBr):** 1650 (>C=O), 1608 (>C=C<), 1157 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ4.97 (s, 2H,-CH<sub>2</sub>Cl), δ7.90 (s,1H, 6Ar-H), δ8.09 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 375.5 (71), 226 (100), 170(57), 97(42), 63(27). Anal. Calcd. For C<sub>8</sub>H<sub>5</sub>O<sub>2</sub>IClBr: C, 25.56; H, 1.33; X, 64.58 %. Found: C, 25.47; H, 1.41; X, 64.44 %.

**2-Chloro-1-(5-chloro-2-hydroxy-3-iodo-phenyl)-ethanone (2d):** Yield 85 %, m.p.83<sup>0</sup>C; **IR (KBr):** 1646 (>C=O), 1600 (>C=C<), 1162 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ4.99 (s, 2H,-CH<sub>2</sub>Cl), δ7.86 (s,1H, 6Ar-H), δ8.05 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 331 (65), 281 (100), 126(60), 91(55), 63(30). Anal. Calcd. For C<sub>8</sub>H<sub>5</sub>O<sub>2</sub>ICl<sub>2</sub>: C, 29.00; H, 1.51; X, 59.81 %. Found: C, 28.87; H, 1.42; X, 59.72 %.

**2-Chloro-1-(2-hydroxy-3,5-diiodo-4,6-dimethyl-phenyl)-ethanone (2e):** Yield 80 %, m.p.113<sup>0</sup>C; **IR (KBr):** 1655 (>C=O), 1610 (>C=C<), 1156 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ5.01 (s, 2H,-CH<sub>2</sub>Cl), δ7.86 (s,1H, 6Ar-H), δ8.05 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 450.5 (59), 401(100), 121(67), 105(48), 77(20), 51(14). Anal. Calcd. For C<sub>10</sub>H<sub>9</sub>O<sub>2</sub>I<sub>2</sub>Cl: C, 26.63; H, 1.99; X, 64.26 %. Found: C, 26.50; H, 2.08; X, 64.11 %.

**1-(2-Hydroxy-3,5-diiodo-4-methyl-phenyl)-propan-1-one (2f):**Yield 78 %, m.p.134<sup>0</sup>C; **IR (KBr):** 1643 (>C=O), 1588 (>C=C<), 1167 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ1.21 (t, 3H,-CH<sub>2</sub>-CH<sub>3</sub>), 2.37(s, 3H, 4Ar-CH<sub>3</sub>), δ3.02 (q, 2H,-CH<sub>2</sub>-CH<sub>3</sub>), δ8.12 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 416 (70), 387(100), 261(44), 105(22), 77(15), 51(14). Anal. Calcd. For C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>ICl: C, 34.78; H, 2.57; X, 52.33 %. Found: C, 34.67; H, 2.48; X, 52.24 %.

**1-(5-Chloro-2-hydroxy-3-iodo-phenyl)-propan-1-one (2g):** Yield 83 %, m.p.158<sup>0</sup>C; **IR (KBr):** 1649 (>C=O), 1585 (>C=C<), 1162 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ1.23 (t, 3H,-CH<sub>2</sub>-CH<sub>3</sub>), δ3.00 (q, 2H,-CH<sub>2</sub>-CH<sub>3</sub>), δ7.85 (s,1H, 6Ar-H), δ8.07 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 310.5 (80), 281(100), 126(34), 91(12), 63(24). Anal. Calcd. For C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>ICl: C, 34.78; H, 2.57; X, 52.33 %. Found: C, 34.64; H, 2.46; X, 52.24 %.

**1-(3-Chloro-2-hydroxy-5-iodo-phenyl)-propan-1-one (2h):** Yield 77 %, m.p.79<sup>0</sup>C; **IR (KBr):** 1651 (>C=O), 1581 (>C=C<), 1167 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ1.24 (t, 3H,-CH<sub>2</sub>-CH<sub>3</sub>), δ3.03 (q, 2H,-CH<sub>2</sub>-CH<sub>3</sub>), δ7.82 (s,1H, 6Ar-H), δ8.03 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 310.5 (64), 281(100), 126(12), 91(08), 63(12). Anal. Calcd. For C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>ICl: C, 34.78; H, 2.57; X, 52.33 %. Found: C, 34.65; H, 2.48; X, 52.21 %.

**1-(2-Hydroxy-5-iodo-3-methyl-phenyl)-propan-1-one (2i):** Yield 80 %, m.p.147<sup>0</sup>C; **IR (KBr):** 1654 (>C=O), 1592 (>C=C<), 1160 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ1.21 (t, 3H,-CH<sub>2</sub>-CH<sub>3</sub>), 2.33(s, 3H, 3Ar-CH<sub>3</sub>), δ3.02 (q, 2H,-CH<sub>2</sub>-CH<sub>3</sub>), δ7.87 (s,1H, 6Ar-H), δ8.10 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 290 (56), 260(100), 106(37), 77(12), 51(09). Anal. Calcd. For C<sub>10</sub>H<sub>11</sub>O<sub>2</sub>I: C, 41.37; H, 3.79; I, 43.79 %. Found: C, 41.50; H, 3.88; X, 43.91 %.

**1-(2-Hydroxy-3,5-diiodo-4,6-dimethyl-phenyl)-propan-1-one (2j):** Yield 83 %, m.p.75<sup>0</sup>C; **IR (KBr):** 1660 (>C=O), 1595 (>C=C<), 1167 (>C-O) cm<sup>-1</sup>; **<sup>1</sup>HNMR (CDCl<sub>3</sub>):** δ1.23 (t, 3H,-CH<sub>2</sub>-CH<sub>3</sub>), 2.35(s, 3H, 6Ar-CH<sub>3</sub>), δ3.05 (q, 2H,-CH<sub>2</sub>-CH<sub>3</sub>), δ7.87 (s,1H, 6Ar-H), δ8.10 (s,1H, 4Ar-H)ppm; **M.S. (m/z, %):** M<sup>+</sup> 430 (60), 401(100), 120(58), 106(41), 77(04), 51(06). Anal. Calcd. For C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>I<sub>2</sub>: C, 30.69; H, 2.79; I, 59.06 %. Found: C, 30.55; H, 2.88; I, 58.97 %.

## RESULTS AND DISCUSSION

In continuation of our earlier research works [20-26] on iodination of some aromatics by using iodine and iodic acid as an iodinating agent, herein, we would like to report a simple and efficient iodination of new substituted  $\alpha$ -Chloro-hydroxyacetophenones and substituted hydroxypropiophenones (Scheme 1).

A combination of iodine and iodic acid has been found to be an excellent reagent for the efficient iodination of carbonyl compounds such as substituted  $\alpha$ -Chloro-hydroxyacetophenones and substituted hydroxypropiophenones. These reactions are carried out at 35-40<sup>0</sup>C using 95% aqueous ethyl alcohol with excellent yields (73-85%, Table 1). A variety of *ortho/para* hydroxy substituted aromatic aldehydes and ketones 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.* -COCH<sub>2</sub>- R or -CH<sub>3</sub>; only nuclear iodination takes place.

## CONCLUSION

In summary, a simple and convenient method for the iodination of new substituted  $\alpha$ -Chloro-hydroxyacetophenones and substituted hydroxypropiophenones. The advantages of this method include easy and simple procedure, no need of catalyst, nearly quantitative yield; chemicals are not hazardous and can be weighed easily.

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