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Working with Hazardous Chemicals

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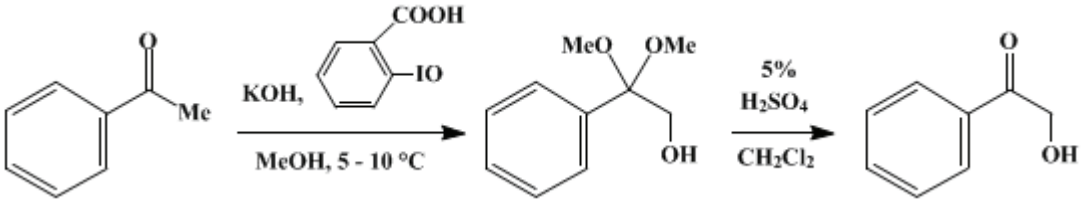
α-HYDROXYLATION OF A KETONE USING *o*-IODOSYLBENZOIC ACID: α-HYDROXYACETOPHENONE VIA THE α-HYDROXY DIMETHYLACETAL

[Ethanone, 2-hydroxy-1-phenyl-]



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Checked by Janice Klunder and K. Barry Sharpless.

1. Procedure

A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, 100-mL pressure-equalized addition funnel to which is attached a drying tube, and a stopper. Anhydrous methanol (80 mL) (Note 1) is added to the flask, which is cooled to 5–10°C. Stirring is begun and 8.4 g (0.15 mol) of powdered potassium hydroxide is added. Acetophenone (6.0 g; 0.05 mol) (Note 2) dissolved in 20 mL of methanol is added dropwise over a period of 10 min. After the solution is stirred for 15 min, 14.52 g (0.055 mol) of *o*-iodosylbenzoic acid (Note 3) is added during 30 min. The ice bath is removed and the resultant yellow-colored slurry is stirred overnight at room temperature to give a clear red solution (Note 4). The mixture is concentrated under reduced pressure in a rotary evaporator until one-half of the methanol is removed, and then 30 mL of water is added followed by extraction with four 50-mL portions of dichloromethane. The combined dichloromethane extracts are washed with two 10-mL portions of water, and the combined organic extracts are dried over anhydrous magnesium sulfate for 1 hr. After filtration, the methylene chloride is removed under reduced pressure in a rotary evaporator, and the crude acetal is distilled to give a fraction at 73–76°C (0.4 mm) weighing 6.0 g (65%) (Note 5). The acetal is of high purity, as shown by spectral analysis (Note 6).

α-*Hydroxyacetophenone*. In a 500-mL, round-bottomed flask equipped with a magnetic stirrer are placed 6.0 g (0.33 mol) of α-hydroxy dimethylacetal and 100 mL of dichloromethane. Stirring is begun and the flask is cooled to about 10°C with ice water. Aqueous 5% sulfuric acid (100 mL) is added dropwise from a pressure-equalized addition funnel and the mixture is stirred for another 30 min. The dichloromethane layer is separated and the aqueous layer is extracted twice with 25-mL portions of dichloromethane. The combined extracts are washed with two 10-mL portions of water and dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure using a rotary evaporator. The resulting yellow crystalline solid is recrystallized from carbon tetrachloride to give a white crystalline material, mp 86–87.5°C (lit.[2] mp 86–87°C), yield 3.7 g (83%) (Note 7).

2. Notes

1. Anhydrous methanol is obtained by treatment with magnesium methoxide, obtained by refluxing 50 mL of methanol, 5 g of magnesium turnings, and 0.5 g of sublimed iodine together until the iodine color disappears. The 1 L of methanol is added and the system is kept at reflux for 1 hr and distilled to yield purified methanol (bp 64.5°C).
2. Acetophenone was used as purchased from Fisher Scientific Company.
3. *o*-Iodosylbenzoic acid was used as purchased from Sigma Chemical Company.
4. TLC (ethyl acetate:hexane) shows residual starting material.
5. The α-hydroxy dimethylacetal obtained must be used immediately in the next step because at room temperature it undergoes a dimerization reaction by loss of two molecules of methanol.

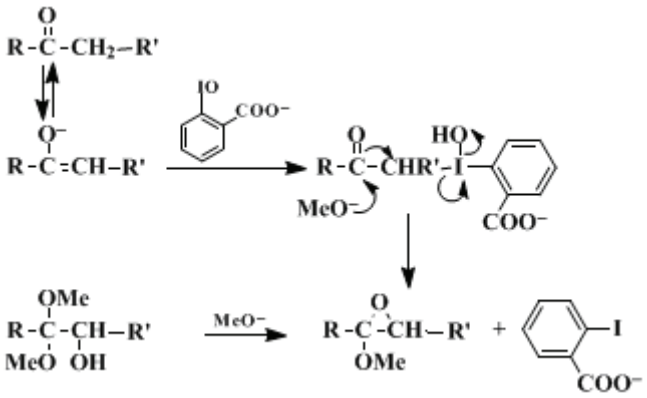
6. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3470 (-OH): ^1H NMR ($CDCl_3$) δ: 1.83 (s, 1 H, OH), 3.23 (s, 6 H, $(OCH_3)_2$), 3.73 (s, 2 H, CH_2), 7.27–7.67 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ: 139.3 (s), 128.4 (d), 127.4, (d) 102.4 (s), 65.3 (t) 49.1 (q); mass spectrum: *m/e* 151 (M^+-OCH_3 100%), 105 (29.7%), 91 (31.7%), 77 (7.0%).
7. The product has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 3.63 (s, 1 H, OH), 4.86 (s, 2 H, CH_2), 7.25–7.90 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ: 198.6 (s), 134.4 (s), 129.1 (d), 127.8 (d), 65.6 (t).

3. Discussion

The procedure reported here provides a convenient method for the α-hydroxylation of ketones that form enolates under the reaction conditions. The reaction has been applied successfully to a series of para-substituted acetophenones, 1-phenyl-1-propanone, 3-pentanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclododecanone, 2-methylcyclohexanone, 2-norbornanone, and benzalacetone.[3] In the case of a steroidal example it was shown that a carbon–carbon double bond and a secondary hydroxyl group are not oxidized.[4] A primary amino function, as in the case of *p*-aminoacetophenone, is not affected.[5] Similarly, a tertiary amino ketone such as tropinone undergoes the α-hydroxylation reaction.[5]

The present procedure using *o*-iodosylbenzoic acid is an improvement over our original method, which uses either iodosylbenzene or diacetoxyphenyliodine(III).[6,7,8] The advantage of the present method is the solubility of the product iodobenzoic acid under the basic reaction conditions. Thus the α-hydroxy dimethylacetal may be isolated by direct extraction. Using the original procedure, both carboxylic acids and esters underwent high yield α-hydroxylation.[8]

The pathway by which the reactions are considered to occur involves attack of the enolate anion at the I=O bond of *o*-iodosylbenzoic acid followed by reductive elimination of *o*-iodobenzoic acid upon addition of methoxide to the carbonyl group. Ring opening of the epoxide thus formed yields the hydroxy dimethylacetal:



Other methods for α-hydroxy ketone synthesis are as follows: addition of $^3O_2$ to an enolate followed by reduction of the α-hydroperoxy ketone using triethyl phosphite;[9] the molybdenum peroxide–pyridine/HMPA oxidation of enolates;[10] photooxygenation of enol ethers followed by triphenylphosphine reduction;[11] the epoxidation of trimethylsilyl enol ethers by peracid;[12] the oxidation of trimethylsilyl enol ethers by osmium tetroxide in *N*-methylmorpholine *N*-oxide;[13] and, finally, the classical method of hydrolysis of an α-bromo ketone.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 132

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

α-HYDROXY DIMETHYLACETAL

hydroxy dimethylacetal

HMPA

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

methanol (67-56-1)

magnesium turnings (7439-95-4)

Cyclohexanone (108-94-1)

carbon tetrachloride (56-23-5)

iodine (7553-56-2)

Benzalacetone (122-57-6)

Acetophenone (98-86-2)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Cyclopentanone (120-92-3)

magnesium methoxide

iodobenzoic acid,
o-iodobenzoic acid (88-67-5)

methylene chloride,
dichloromethane (75-09-2)

1-phenyl-1-propanone (93-55-0)

magnesium sulfate (7487-88-9)

α-Hydroxyacetophenone,
Ethanone, 2-hydroxy-1-phenyl- (582-24-1)

3-pentanone (96-22-0)

osmium tetroxide (20816-12-0)

iodosylbenzene (536-80-1)

hexane (110-54-3)

2-methylcyclohexanone (583-60-8)

Cycloheptanone (502-42-1)

tropinone (532-24-1)

Triethyl phosphite (122-52-1)

triphenylphosphine (603-35-0)

cyclododecanone (830-13-7)

2-Norbornanone (497-38-1)

diacetoxyphenyliodine(III)

molybdenum peroxide

N-methylmorpholine N-oxide (80913-66-2)

p-aminoacetophenone (99-92-3)

o-IODOSYLBENZOIC ACID (304-91-6)