Hypervalent Iodine Oxidation of Enol Silyl Ethers using Boron Trifluoride Etherate. A Direct Route to Aryl Hydroxymethyl Ketones

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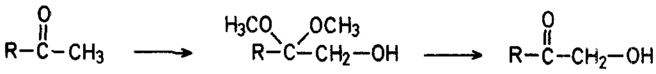
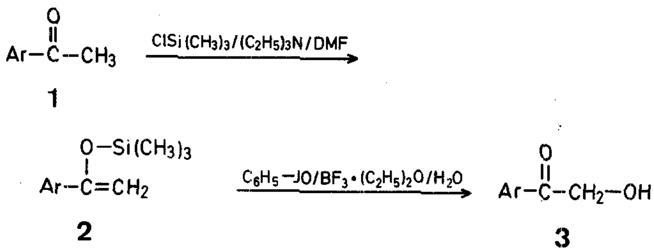
Enol silyl ethers of acetophenones and acetylpyridines are oxidized to hydroxymethyl aryl ketones (ω-hydroxyacetophenones) and hydroxyacetylpyridines, respectively, using the system iodosobenzene/boron trifluoride etherate/water.

Treatment of enolizable ketones with idosobenzene/methanol/potassium hydroxide leads to efficient formation of α-hydroxyketone dimethyl acetals[1].



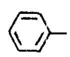
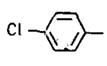
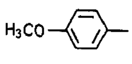
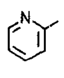
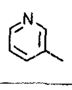
Scheme A

In some cases, the dimethyl acetal itself is a useful compound for subsequent transformations[2,3]. Hydrolysis of the dimethyl acetal may yield the α-hydroxyketone but a direct route is desirable. We now report such a direct route (Scheme B) to aryl hydroxymethyl ketones (3). The methyl ketones 1 are converted into the enol silyl ethers by the method of Ref.[4]; treatment of compounds 2 with iodosobenzene, boron trifluoride etherate, and water in ether or dichloromethane affords the hydroxymethyl ketones 3 in good yields.



Scheme B

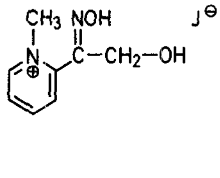
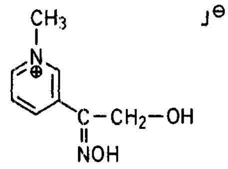
Table. Aryl (and Pyridinyl) Hydroxymethyl Ketones (3) prepared according to Scheme B

3	Ar	Yield[a] [%]	m.p. [°C]	Molecular Formula[b] or m.p. [°C] reported
a		57	86–87°	86–88°[7]
b		63	121–122°	122–123°[8]
c		65	105–106°	105–106°[9]
d		45	70–71°	$C_7H_7NO_2$ (137.1)
e		38	112–113°	$C_7H_7NO_2$ (137.1)

[a] Yield of isolated pure product with respect to the quantity of iodosobenzene used.

[b] For analyses and spectral data, see procedures.

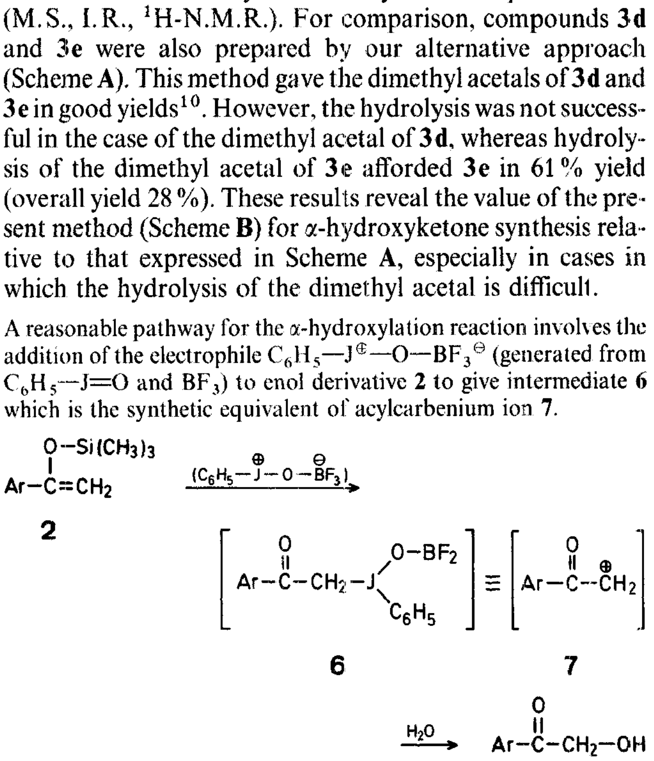
The conversion **2** → **3** is significant for the following reasons:
- the α-hydroxyketones **3** are obtained in a single step and the procedure consists of very simple experimentation[5];
- 2- and 3-hydroxyacetylpyridine (**3d, e**) are potentially valuable intermediates for the synthesis of oxime methiodides **4** and **5**, respectively, which are useful as acetylcholinesterase reactivators[6];
- the N-atoms in compounds **3d** and **3e** are not oxidized under the reaction conditions.

4 **5**

The structures of products **3a, b, c** are based upon comparison with authentic samples[7,8,9]. The compounds **3d** and **3e** were characterized by microanalyses and spectral data (M.S., I.R., ^{1}H-N.M.R.). For comparison, compounds **3d** and **3e** were also prepared by our alternative approach (Scheme **A**). This method gave the dimethyl acetals of **3d** and **3e** in good yields[10]. However, the hydrolysis was not successful in the case of the dimethyl acetal of **3d**, whereas hydrolysis of the dimethyl acetal of **3e** afforded **3e** in 61% yield (overall yield 28%). These results reveal the value of the present method (Scheme **B**) for α-hydroxyketone synthesis relative to that expressed in Scheme **A**, especially in cases in which the hydrolysis of the dimethyl acetal is difficult.

A reasonable pathway for the α-hydroxylation reaction involves the addition of the electrophile $C_6H_5—J^{\oplus}—O—BF_3^{\ominus}$ (generated from $C_6H_5—J{=}O$ and BF_3) to enol derivative **2** to give intermediate **6** which is the synthetic equivalent of acylcarbenium ion **7**.



This sequence may be viewed as an umpolung of the enolate anion. Of course we do not wish to imply that a carbenium ion is actually involved in reaction **6** → **3**. The details of the carbon-iodine bond cleavage are presently unknown.

Aryl Hydroxymethyl Ketones (3a–e); General Procedure:

Boron trifluoride etherate (1.42 g, 0.01 mol) is dissolved in dichloromethane or ether (100 ml) and iodosobenzene (1.1 g, 0.005 mol) is added. The mixture is stirred, cooled to −40 °C, and then the enol silyl ether **2** (0.006 mol) is added, followed by water (2 ml). The mixture is stirred at −40 °C for 1 h and then the temperature is slowly raised (over 1 h) to room temperature. Stirring is continued for 30 min, the solution then transferred to a separatory funnel, and washed with water (2 × 25 ml) and sodium hydrogen carbonate solution (25 ml). The combined washings (the organic phase is saved) are extracted with dichloromethane (3 × 25 ml). The organic phases are combined, dried with magnesium sulfate, and concentrated in vacuo. The pure products **3a, b, c, e** are obtained by direct crystallization. Product **3d** is purified by column chromatography on silica gel using ether/hexane (40/60) as eluent.

2-Hydroxyacetylpyridine (**3d**):

$C_7H_7NO_2$	calc.	C 61.31	H 5.15	N 10.22
(137.1)	found	61.10	5.19	10.16

M.S. (70 eV): m/e = 137 (M$^+$, 40%), 107 (88), 106 (35), 79 (95), 78 (100).

I.R. (Nujol): ν = 1720 (C=O str); 3510 (O—H str) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 3.30 (br., 1H, OH; disappears with D_2O); 5.13 (s, 2H, CH_2—OH); 7.30–8.72 ppm (m, 4$H_{pyridine}$).

3-Hydroxyacetylpyridine (**3e**):

$C_7H_7NO_2$	calc.	C 61.31	H 5.15	N 10.22
(137.1)	found	61.20	5.21	10.12

M.S. (20 eV): m/e = 137 (M$^+$, 5%), 107 (11), 106 (100), 79 (13), 78 (92).

I.R. (KBr): ν = 1715 (C=O str); 3500 (O—H str) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 3.45 (br., 1H, OH; disappears with D_2O); 4.95 (s, 2H, CH_2—OH); 7.32–9.10 ppm (m, 4$H_{pyridine}$).

3-Hydroxyacetylpyridine (3e); Preparation according to Scheme A:

3-(2-Hydroxy-1,1-dimethoxyethyl)-pyridine: 3-Acetylpyridine is oxidized with diacetoxyphenyliodine/potassium hydroxide/methanol as described in Ref.[10]; yield: 45%; m.p. 88–89 °C.

3-Hydroxyacetylpyridine (**3e**): 3-(2-Hydroxy-1,1-dimethoxyethyl)-pyridine (0.91 g) is dissolved in water (10 ml) and 6 normal hydrochloric acid (20 ml) is added with stirring. The resultant solution is kept at room temperature for 20 h. The solution is then made alkaline with aqueous sodium hydrogen carbonate, saturated with ammonium chloride, and extracted with chloroform (5 × 40 ml). The combined extracts are dried with magnesium sulfate and concentrated in vacuo. The remaining product is recrystallized from acetone; yield of pure **3e**: 0.42 g (61%); m.p. 112–113 °C; mixture m.p. with **3e** prepared according to Scheme **B**, 112–113 °C. The spectral data of products **3e** prepared according to Schemes **A** and **B** were identical.

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