

α -Hydroxylation of carbonyls using iodine

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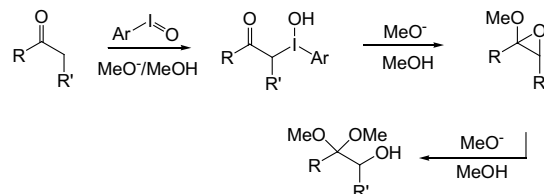
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Abstract—The α -hydroxylation of ketones and aldehydes to α -hydroxyketals mediated by iodine under basic conditions in MeOH is described. Enolates generated under the reaction conditions are iodinated and the resulting α -iodocarbonyl is transformed into the hydroxyketal. The use of iodine for this chemistry represents an economical and practical alternative to existing methods for this transformation.

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α -Hydroxy carbonyls are versatile synthetic intermediates that are useful for the preparation of 1,2-aminoalcohols,¹ α -aminocarbonyls,² and 1, 2-diols.³ In addition to their utility as synthetic precursors, α -hydroxy carbonyls are important substructures present in a wide variety of natural products and pharmaceutically important compounds.⁴ Consequently, this motif has attracted considerable attention from the synthetic community. A powerful method for their preparation from the parent carbonyl involves the hydroxylation of preformed enolates or enol ethers with a variety of oxidizing agents, including peroxyacids,⁵ OsO₄,⁶ MoOPh,⁷ oxaziridines,⁸ and DMDO.⁹ Recently a number of reports have described the proline-catalyzed asymmetric α -oxyamination of ketones and aldehydes using nitroso-benzene as the oxidant.¹⁰ An alternative approach involves the one step formation of α -hydroxyketals from the corresponding carbonyl via the hydroxylation of enolates formed in situ. This strategy largely involves the use of hypervalent iodine reagents such as iodoso-benzene, (diacetoxy)iodobenzene, and *o*-iodosylbenzoic acid.¹¹ These reactions proceed via an intermediate epoxide, and bear mechanistic similarity to the traditional method of treating preformed α -halo ketones with alkoxides (Scheme 1).¹²

We recently required a practical synthesis of an α -hydroxy ketal and were intrigued by the possibility of finding a surrogate for the established hypervalent iodine reagents. In particular, we wondered whether I₂ could

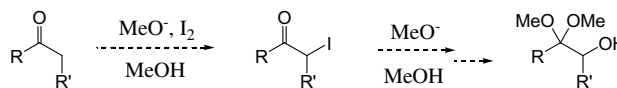


Scheme 1.

accomplish the same one step transformation (Scheme 2).

While the α -hydroxylation of ketones using electrochemically generated halogens is known,^{2a,13} we are unaware of any efforts that utilize elemental iodine as a reagent for this reaction. Furthermore, the impracticality of conducting electrochemistry on a multi-kilogram scale warranted an investigation of the use of I₂.

One advantage of such a process would be the elimination of iodobenzene as a by-product, which can be difficult to remove from a non-crystalline product without resorting to column chromatography. Another advantage would be the dramatically reduced cost of the oxidizing reagent, which is particularly pronounced on scale. Lastly, any potential safety hazards associated


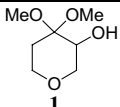

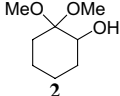

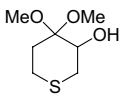

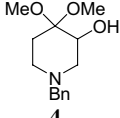

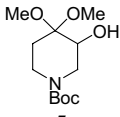

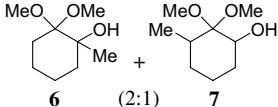


Scheme 2.

Keywords: α -Hydroxylation; Iodine; Acyloins.

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Table 1. α -Hydroxylation of cyclic ketones

Entry	Ketone	Product	Isolated yield (%)
1		 1	89
2		 2	85
3		 3	81
4		 4	50
5		 5	80
6		 6 (2:1) 7	75

All reactions performed by addition of a 0.6 M solution of I_2 /MeOH over 1.5 h to a 0.5 M solution of ketone in MeOH containing 2.4 equiv of KOH (0–5 °C).

with iodoso compounds would be avoided.¹⁴ We report herein the successful employment of I_2 for the α -hydroxylation of aldehydes and ketones, including the scope and limitations of this reaction.

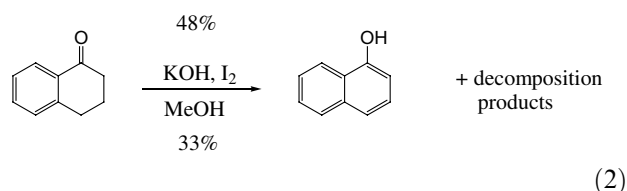
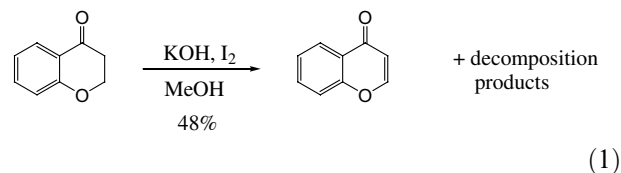
Our studies began with the investigation of ketones in the proposed α -hydroxylation reaction. Addition of 1.0 equiv of solid I_2 in one portion to a room temperature solution of tetrahydro-4*H*-pyran-4-one in MeOH with 2.0 equiv of KOH led to the formation of the desired α -hydroxyketal **1** in 53% yield. The use of Br_2 instead of I_2 failed to afford any trace of **1**. After experimenting with a variety of reaction conditions, we discovered that a controlled addition of a MeOH solution of I_2 to the KOH/MeOH solution containing the ketone led to higher yields. Furthermore, cooling the reaction temperature led to improved efficiency of the reaction. The optimized conditions involved the addition of an I_2 /MeOH solution (1.1 equiv of I_2) over 1.5–2 h to a 0–5 °C solution containing 2.4 equiv of KOH, MeOH, and the ketone, affording **1** in 89% yield. These conditions were applied to a series of 6-membered ring cyclic ketones and the results are summarized in Table 1.¹⁵

Tetrahydropyranone, tetrahydrothiopyranone, and piperidone heterocycles are well tolerated, as well as a Boc-protected amine. We speculate that the presence of a basic amine is likely responsible for the lower yield of **4** (Table 1, entry 4) relative to that of **5** (Table 1, entry

5). Entry 6 reflects the enolate equilibrium under the reaction conditions, and highlights the ability to form tertiary alcohols using this process. Acyclic ketones did not react to afford the corresponding α -hydroxyketals. Instead, esters resulting from a Favorskii rearrangement were obtained.

Entry 1 (Table 1) demonstrates the benefits of using I_2 and thus avoiding the production of organic by-products. Upon completion of the I_2 addition, the reaction was stirred for 1 h at room temperature. Following the removal of MeOH and the addition of toluene, the inorganic KI was removed by filtration, and the filtrate was concentrated to afford pure **1**.

Attempts to extend this reaction to conjugated 6-membered ring ketones were unsuccessful due to the propensity of the intermediate α -iodoketone to undergo elimination. For example, subjection of chromanone to the conditions established for the synthesis of **1** led to a complex mixture of products, of which chromone was the major product isolated in 48% yield (Eq. 1). Likewise, α -tetralone led to a complex mixture, of which 1-naphthol was the major product isolated in 33% yield (Eq. 2). Subjection of 2-iodotetralone¹² to the reaction conditions led to an identical reaction profile.



The ring size of the cyclic ketone had a dramatic effect on the efficiency of the α -hydroxylation. For example, cyclopentanone reacted to form an intermediate α,α -diiodoketone, giving rise to a complex mixture including 2,2-dimethoxycyclopentanone as the major product (Eq. 3).¹⁶ The reactivity of cycloheptanone demonstrated that 7-membered rings follow both mono- and diiodination pathways. Reaction of 1.1 equiv of I_2 with cycloheptanone gave rise to a 2.2:1 mixture of the desired α -hydroxyketal **8** and methyl-1-cyclohexene-1-carboxylate (**9**),¹⁶ the latter likely resulting from a Favorskii rearrangement of an initially formed α,α -diiodoketone followed by elimination (Eq. 4).¹⁷ Variation of the rate of I_2 addition did not affect this ratio.

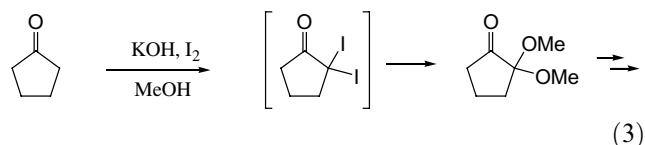
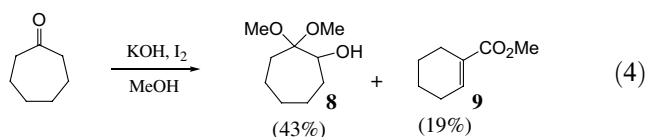


Table 2. α -Hydroxylation of aldehydes

Entry	Aldehyde	Product	Temp (°C)	Time (h) ^a	Isolated yield (%)
1			–10	1	72
2			–10	1	50
3	$\text{CH}_3(\text{CH}_2)_7\text{CHO}$		0	0.5	75
4			rt	0.5	77
5			rt	0.5	80

^a Time of I₂ addition.

We next turned our attention towards the α -hydroxylation of aldehydes (Table 2).¹⁸ Variations in the structure of the aldehyde required minor adjustments of the reaction parameters in order to obtain optimal yields. The lower yield of **12** (Table 2, entry 2) reflects the instability of phenylacetaldehyde towards basic conditions, evidenced by the observation of various aldehyde polymerization products by ¹H NMR. Entry 5 is significant in that the 4-piperidinol substructure is an important pharmaceutical moiety,¹⁹ and thus **15** may serve as a valuable synthetic building block.

In summary, we have described the iodine-mediated α -hydroxylation of cyclic 6-membered ring ketones and aldehydes to α -hydroxyketals in good yield. The described process offers advantages over existing methods for the synthesis of these valuable compounds in terms of practicality, cost, and waste. This process also provides superior yields of α -hydroxyketals relative to the use of hypervalent iodine reagents or of electrochemical conditions. Studies aimed at further definition of the scope of this hydroxylation chemistry are underway and will be reported in due course.

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15. General experimental procedure for the synthesis of 1–7: To a 0–5 °C solution of 24.0 mmol KOH (1.6 g of A.C.S. reagent pellets, 85% KOH assay) in 21 mL of anhydrous MeOH was added the ketone (10.0 mmol) over several minutes. Following a 5–10 min age, a solution of I₂ (2.8 g, 11.0 mmol) in 18.5 mL of MeOH was added over 1.5 h. Upon completion of the addition, the solution was gradually warmed to room temperature and aged for an additional hour. The resulting solution was then concentrated, and 50 mL of PhMe was added and the resulting slurry was filtered. Concentration afforded the crude α -hydroxyketal, which was suitable for further use, but could be purified by silica gel chromatography. Data for 3: ¹H NMR (CD₃OD, 400 MHz) δ 3.94 (dd, J_1 = 2.1 Hz, J_2 = 4.8 Hz, 1H), 3.29 (s, 3H), 3.25 (s, 3H), 3.11 (dd, J_1 = 2.0 Hz, J_2 = 13.8 Hz, 1H), 2.76–2.69 (m, 1H), 2.64–2.58 (m, 1H), 2.44–2.38 (m, 1H), 2.05–2.01 (m, 2H); ¹³C NMR (CD₃OD, 400 MHz) δ 100.5, 67.1, 48.2, 47.6, 33.9, 30.6, 25.7; Anal. Calcd for C₇H₁₄O₃S: C, 47.17; H, 7.92; S, 17.99. Found C, 46.91; H, 7.84; S, 17.69. Data for 4: ¹H NMR (CD₃OD, 400 MHz) δ 7.41–7.28 (m, 5H), 3.73–3.71 (m, 1H), 3.59 (d, J = 12.9 Hz, 1H), 3.52 (d, J = 12.9 Hz, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 2.79–2.72 (m, 1H), 2.67–2.60 (m, 1H), 2.49–2.45 (m, 1H), 2.27–2.19 (m, 1H), 1.99–1.91 (m, 1H), 1.82–1.77 (m, 1H); ¹³C NMR (CD₃OD, 400 MHz) δ 139.1, 130.7, 129.4, 128.4, 100.4, 69.0, 63.5, 57.6, 50.8, 48.5, 48.1, 28.9; Anal. Calcd for C₁₄H₂₁O₃N: C, 66.91; H, 8.42; N, 5.57. Found C, 66.95; H, 8.43; N, 5.53. Data for 5: ¹H NMR (CD₃OD, 400 MHz) δ 4.06–4.00 (m, 1H), 3.99–3.91 (m, 1H), 3.80–3.73 (m, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 3.22–3.10 (br m, 1H), 2.95–2.80 (br m, 1H), 1.91–1.77 (m, 2H), 1.50 (s, 9 H); ¹³C NMR (CD₃OD, 400 MHz) δ 158.0, 100.5, 81.0, 67.7, 48.3, 47.9, 42.0, 41.0, 28.8, 28.2; Anal. Calcd for C₁₂H₂₃O₅N: C, 55.16; H, 8.87; N, 5.36. Found: C, 55.14; H, 9.01; N, 5.31. For characterization of 1: Ref. 2a For characterization of 2, 6 and 7 see Ref. 10e and citations therein.
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