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# Mild Oxidation of Aldehydes to the Corresponding Carboxylic Acids and Esters: Alkaline Iodine Oxidation Revisited

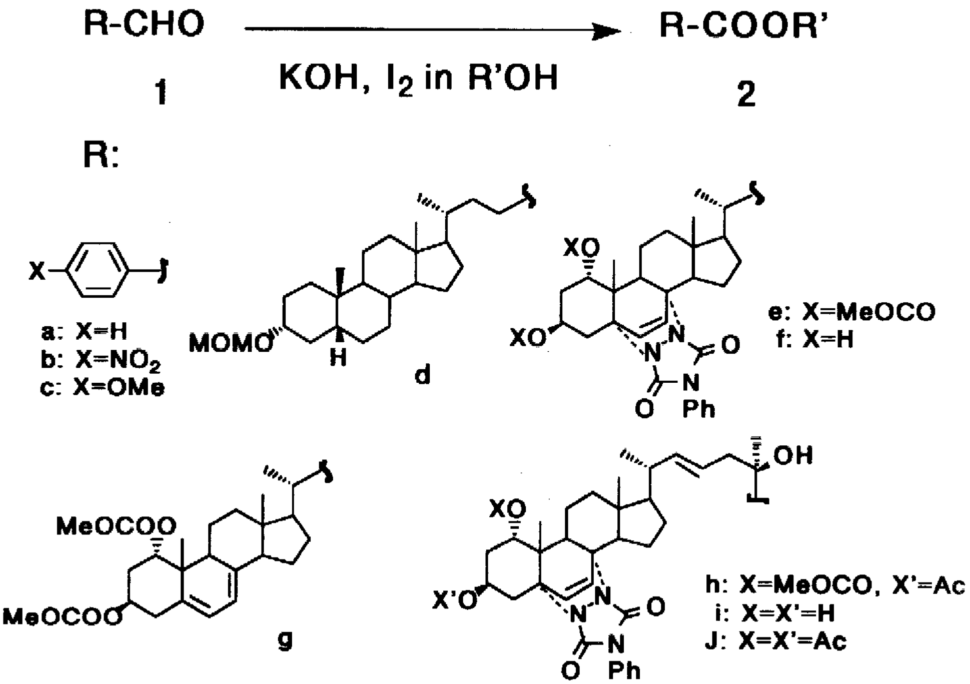
**Sachiko Yamada,* Daisuke Morizono, and Keiko Yamamoto**

Institute for Medical and Dental Engineering, Tokyo Medical and Dental University
2-3-10 Surugadai, Kanda, Chiyoda-ku, Tokyo 101, Japan

**Abstract:** The classical alkaline iodine oxidation used in the quantification of aldoses was developed to a synthetically useful, mild, efficient, and general method for oxidizing aldehydes to the corresponding carboxylic acids and esters and the mechanism of the reaction was discussed.

Oxidation of aldehydes to the corresponding carboxylic acids occurs easily by autooxidation. However we often have difficulties in synthesizing carboxylic acids from the corresponding aldehydes, especially when the aldehydes have complex functional groups in the molecule. Use of heavy metallic oxidants sometimes results in unsatisfactory overall recovery of the material. Halogen compounds known as mild oxidants such as hypochlorites,[1] chlorites,[2] and NBS,[3] are not compatible with olefinic bonds, secondary hydroxyl group, and electron rich aromatic ring systems. During the synthesis of γ,δ-unsaturated carboxylic acid (**2i**, R'=H) from aldehyde **1j** we found that treatment of **1j** with alkaline solution of iodine in MeOH gave the corresponding methyl ester (**2j**, R'=Me) in high yield.[4] Alkaline solution of iodine is a classical oxidant used in the quantification of aldoses,[5] but the mechanism of the reaction has not been clearly understood and the oxidation has not been used in general organic synthesis. We investigated the oxidation in detail from synthetic points of view. Here we report a new mild, efficient, and general method for oxidizing aldehydes to the corresponding carboxylic acids and esters.

In a typical method, aldehyde **1d** (0.3 mmol) was dissolved in methanol (4 mL) and solutions of KOH (2.6 equiv.) and iodine (1.3 equiv.) in MeOH (each 1 mL) were successively added at 0°C.[6] The oxidation was completed in 10 min to give **2d** (R'=Me)[7] in 98% yield after work up and chromatographic purification. As summarized in Table 1, most aliphatic as well as aromatic aldehydes were oxidized to the corresponding methyl esters in excellent yields. In these oxidations, at least two equivalents (relative to the iodine) of the base were necessary to give the best results (entries 1-3). The oxidation proceeded similarly in EtOH or in 2-PrOH to yield the corresponding ethyl or isopropyl ester, respectively (entries 5-7,12,13). However, the efficiency of the reaction was decreased in the order of MeOH>EtOH>2-PrOH. For example, in the reaction of p-nitrobenzaldehyde, the oxidation completed in 1 min in MeOH, but in EtOH it ceased at 2 min with 95% conversion (entry 5), and in 2-PrOH at 2 min with 75% conversion (entry 6). This is probably because hypoiodous acid (HOI), a presumed active oxidant, is rapidly converted to inactive $KIO_3$ (equations 1-3)[8] in



Scheme 1.

these solvents.[9] The oxidation can be completed by adding excess reagents (entry 7). When the reaction was conducted in aqueous solvent, such as $H_2O$/MeCN (1:1), the carboxylic acid was obtained in high yield (entry 8), in this case additional one equivalent of the base being required to complete the oxidation. Both steric and electronic effects were observed in the oxidation. In the reaction of aromatic aldehydes, *p*-nitro group greatly accelerated (entry 4) while *p*-methoxy group retarded the oxidation (entry 9). The oxidations of sterically hindered aldehydes **1e** and **1f** (entries 14,15) were much slower than that of **1d** (entry 11). But it is interesting to note that the rate of the oxidation of tertiary aldehyde **1h** (entry 16) was faster than that of secondary aldehydes **1e** and **1f**. Under the oxidation conditions, isolated olefinic bonds (entries 14-16) and secondary hydroxyl groups (entry 15) were intact, an asymmetric center adjacent to a formyl group was not epimerized (entry 14), and α-hydroxy aldehyde (**1h**) was converted in high yield to the α-hydroxycarboxyl ester (**2h** R'=Me) (entry 16). However the conjugated endocyclic diene function in **1g** was not tolerable under the conditions of the oxidation, complex mixture being produced.

In the classic method for quantifying aldoses, the aldehyde function is oxidized by iodine in aqueous alkaline solution and the iodine remained is quantified by iodometry. Hypoiodous acid is suggested to be the active oxidant but molecular mechanism of the oxidation of the aldehyde has not been known. On the bases of the results described above, we suggest the mechanism shown in Scheme 2. The hemiacetals (or hydrates) (3) are supposed to be the substrates to be oxidized by the reagent.[10,11] This is supported by the fact that the rate of the oxidation is well related to the concentration of the hemiacetals (hydrates) in the equilibrium.[12] Hypoiodous acid is deprotonated by the base and the resulting hypoiodite would dehydrogenate the hemiacetal as shown in the Scheme.

Table 1. Oxidation of Aldehydes by Alkaline Solution of Iodine

| entry | RCHO (1) | conditions | | | | RCOOR' (2) |
|---|---|---|---|---|---|---|
| | | solvent (R'OH) | KOH equiv. | $I_2$ equiv. | time[a] min | (% yield) |
| 1 | **1a** | MeOH | 2.6 | 1.3 | 60 | 98[b] |
| 2 | **1a** | MeOH | 3.9 | 1.3 | 60 | 92[b] |
| 3 | **1a** | MeOH | 1.3 | 1.3 | 120 | 14[b,c] |
| 4 | **1b** | MeOH | 2.6 | 1.3 | 1 | 98 |
| 5 | **1b** | EtOH | 2.6 | 1.3 | 2 | 95[b,c] |
| 6 | **1b** | 2-PrOH | 2.6 | 1.3 | 2 | 75[b,c] |
| 7[d] | **1b** | 2-PrOH | 2.6+2.6 | 1.3+1.3 | 5+10 | 95 |
| 8[d] | **1b** | $H_2O$/MeCN (1:1) | 2.6+1.0 | 1.3 | 15+5 | 95 |
| 9 | **1c** | MeOH | 2.6 | 1.3 | 60 | 79[b,c] |
| 10 | **1c** | MeOH | 6.0 | 3.0 | 120 | 97 |
| 11 | **1d** | MeOH | 2.6 | 1.3 | 10[e] | 98 |
| 12 | **1d** | EtOH | 2.6 | 1.3 | 30 | 67[c] |
| 13 | **1d** | 2-PrOH | 2.6 | 1.3 | 30 | 49[c] |
| 14 | **1e** | MeOH | 2.6 | 1.3 | 90 | 91[c] |
| 15 | **1f**[f] | MeOH | 2.6 | 1.3 | 90 | 91[c] |
| 16 | **1h** | MeOH | 2.6 | 1.3 | 30 | 94 |

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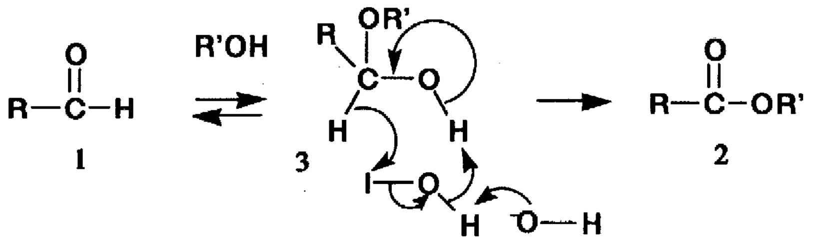
[a] The reactions were conducted under the conditions described in the text and they were terminated at the time indicated. [b] HPLC yield. [c] The starting aldehyde was the only compound detected other than 2. [d] After the indicated (left) time period the additional reagents were added and the reaction was continued for indicated (right) period. [e] The reaction might be completed earlier than the indicated time, since the progress of the reaction was not checked before that time. f) A mixture of C(20) epimers.



Scheme 2.

$$I_2 + KOH \rightleftharpoons KI + HOI \quad (1)$$

$$HOI + KOH \rightleftharpoons KOI + H_2O \quad (2)$$

$$3KOI \rightleftharpoons KIO_3 + 2KI \quad (3)$$

Equations 1-3.

We developed the classical alkaline iodine oxidation to a synthetically useful method for oxidizing aldehydes to the corresponding carboxylic acid derivatives.[11] The method, we believe, is superior to the well known hypochlorite method.[1] Scope and limitation as well as details of the mechanism of the reaction are under investigation in our laboratory.

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6. KOH and $I_2$ should be added separately and rapidly, since the active oxidant (HOI) produced from KOH and $I_2$ is not stable, but the order of addition can be reversed.
7. The structures of new compounds were confirmed by their spectral data: $^1$H NMR ($CDCl_3$) $\delta$, **2e** (R'=Me): 0.84 (3 H, s), 1.06 (3 H, s), 1.19 (3H, d, J=6.9 *Hz*), 3.63 (3 H, s), 3.73 (3 H, s), 3.75 (3 H, s), 4.88 (1 H, m), 5.91 (1 H, m), 6.34 (1 H, d, J=8 *Hz*), 6.43 (1 H, d, J=8 *Hz*); **2h** (R'=Me): 0.83 (3 H, s), 1.01 (3 H, d, J=6.4 *Hz*), 1.07 (3 H, s), 1.38 (3 H, s), 2.01 (3 H, s), 3.73 (3 H, s), 3.77 (3 H, s), 4.87 (1 H, m), 5.94 (1 H, m).
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9. When solutions of iodine and KOH in EtOH or in 2-PrOH were mixed, the brown color of iodine was breached instantaneously, while in MeOH pale brown color remained for hours.
10. Intermediacy of hemiacetals has also been suggested in the oxidation of aldehydes to the corresponding methyl esters with sodium hypochlorite in MeOH.[1a]
11. Electrochemical oxidation of aldehydes in the presence of KI (or KBr) in MeOH (or n-BuOH) has been reported to give the corresponding esters in high yields. The authors proposed halogen cation as an oxidant and hemiacetal and its hypohalite as intermediates. Shono, T.; Matsumura, Y.; Hayashi, J.; Inoue, K.; Iwasaki, F.; Itoh, T. *J. Org. Chem.* **1985**, 50, 4967-4969.
12. The hemiacetal contents of **1a**, **1b**, and **1c** in an equilibrium (25°C) in $CD_3OD$ (determined by the $^1$H NMR spectra) were 6, 78, and 0.5%, respectively.

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