

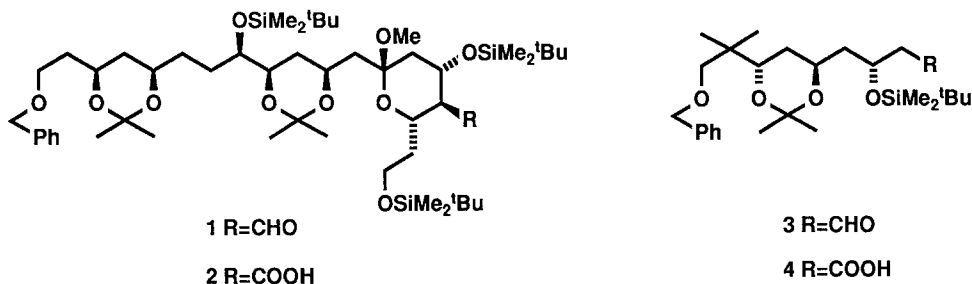
KMnO₄ REVISITED: OXIDATION OF
ALDEHYDES TO CARBOXYLIC ACIDS IN THE
tert-BUTYL ALCOHOL - AQUEOUS NaH₂PO₄ SYSTEM

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Abstract: Aldehydic compounds with one or more protected hydroxyl groups are effectively oxidized with KMnO₄ to the corresponding carboxylic acids using a mixture of t-BuOH and aqueous NaH₂PO₄ as a reaction medium.

Several oxidants are commonly used to convert aldehydes to carboxylic acids.¹ This seemingly simple conversion, however, is by no means straightforward with a highly oxygenated system such as **1**, and a variety of side reactions concurrently take place. For instance, reaction of **1** with either the Jones reagent or RuCl₃(H₂O)_n-NaIO₄² provides a complex mixture of products apparently differing in the oxidation state and site, and



the yields of the corresponding carboxylic acid **2**³ are less than 20% in both cases. On the other hand, **1** slowly decomposes into an uncharacterized product with AgO.⁴ Pressed by the need for an oxidant capable of achieving a "clean" conversion of **1** to **2** as well as **3** to **4**,³ we have examined the reaction conditions commonly used for several reagents, in particular KMnO₄. As outlined below, the simple selection of a t-BuOH-aqueous NaH₂PO₄ mixture as a reaction medium may render this reagent, KMnO₄, widely applicable in the synthesis of complex natural products. This modification is devised in light of the observation that the KMnO₄ oxidation of aliphatic aldehydes shows general-acid catalysis over the pH range 2.80-6.86.⁵

A set of experiments was carried out first to define a standard procedure for this oxidation using the aldehyde **5** as a substrate. Thus, a solution of **5** (0.5 mmol) in t-BuOH (3 mL) was diluted with an aqueous 1.25 M potassium phosphate buffer solution (2 mL) adjusted to a certain pH value and to the resulting solution was added, with vigorous stirring, an aqueous 1 M KMnO₄ solution (3.0 mL) at room temperature.

Table 1 Oxidation of aldehyde 5 to carboxylic acid 6^a

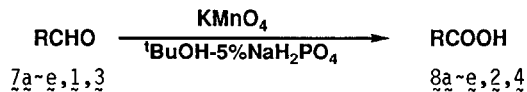
entry	pH of buffer added	reaction time	yield of <u>6</u> (%)	recovered <u>5</u> (%)
1	2.0	20 min ^e	43	45
2	3.7	10 min	95	
3	4.4 ^b	2 min	95	
4	5.0	2 min	95	
5	6.0	2 min	96	
6	7.0	2 min	96	
7	10.0	10 min	91	
8	12.0	40 min ^e	90	5
9	c	6 min	86	
10	d	4 h	38	56

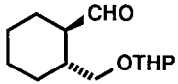
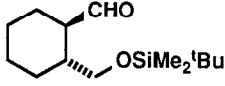
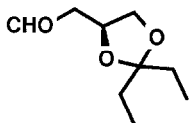
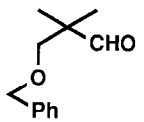
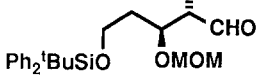
^a See the text for the reaction conditions. ^b 5% NaH₂PO₄ (2 mL) used. ^c H₂O used instead of a phosphate buffer solution. ^d Solid KMnO₄ added. ^e All of the KMnO₄ consumed by the end of the specified reaction time.

After a certain reaction time, the oxidation was quenched by the addition of a saturated solution of Na₂SO₃ and the resulting pH of the mixture was adjusted to 3 with cold (0°C) dilute HCl to dissolve the colloidal MnO₂. The usual extractive workup followed by flash chromatography on silica gel provided the carboxylic acid 6, and in some cases with recovered 5.

Table 1 summarizes the results. With a buffer solution of pH 4.4, 5.0, 6.0, or 7.0, the oxidation of 5 to 6 is brought to completion in excellent yields (entries 3-6). In the pH 2 and 12 experiments (entries 1 and 7) KMnO₄ auto-decomposes rapidly, the aldehyde 5 being partially recovered. Note the amount of the phosphate used in the oxidation is small, yet is still sufficient to prevent the hydroxide produced from causing deleterious effects. In the absence of water, the oxidation proceeds much more slowly⁶ (entry 9), and this result may be compared with three known procedures as applied to the conversion of 5 to 6: (1) KMnO₄ (1 equiv) and dicyclohexyl-18-crown-6 in benzene (reaction conditions, 36 h at room temperature),⁷ yield of 6, 46% and recovery of 5, 42%; (2) Bu₄NMnO₄ (2-3 equiv) in pyridine (2 h at room temperature),⁸ 6, 73% and 5, 17%; (3) NaMnO₄·H₂O (5 equiv) in hexane (3 h under reflux),⁹ 6, 29% and 5, 63%.

In a second set of experiments we have examined the extent to which various protected hydroxyl groups survive under the conditions specified in Table 1, entry 3, which appeared most suitable for this purpose. The substrates are 7a-e, 1 and 3. As Table 2 indicates, the aldehydes having an acetonide, benzyl ether,¹⁰ tetrahydropyranyl ether, methoxymethyl

Table 2 Oxidation of aldehydes 7a-e, 1, and 3 to the corresponding carboxylic acids^a

entry	substrate	reaction time (min)	yield (%)	
1		<u>7a</u>	10	98
2		<u>7b</u>	10	95
3		<u>7c</u>	10	98
4		<u>7d</u>	10	99
5		<u>7e</u>	5	98
6	<u>3</u>	5	97	
7	<u>1</u>	40	80-85	

^a Conditions specified in Table 1, entry 3.

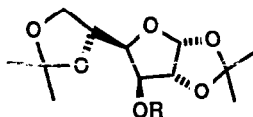
ether and/or silyl ether are smoothly and rapidly converted to the corresponding carboxylic acids (entries 1-5). Thus, through this modified version of KMnO_4 oxidation the synthetic intermediates 2 and 4 described in the introduction are now in our possession.¹¹

A variety of reliable oxidizing reagents for the conversion of "sensitive" alcohols to aldehydes or ketones are available, but for the oxidation of "sensitive" aldehydes to carboxylic acids there are only a few. In view of its operational simplicity, efficiency, and selectivity, the modified method described above will hopefully prove to be of wide synthetic utility.

Acknowledgements. We thank the National Institutes of Health (CA 37804) for financial support.

References and Footnotes

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- (10) Benzyl ethers are slowly oxidized, e.g., three hours' exposure of 9 to this KMnO₄-NaH₂PO₄ at room temperature led to the formation of the cleavage product 10 (24%) with the recovery of 9 (76%).



9: R=CH₂Ph

10: R=H

- (11) ¹H NMR spectra of 2 (400MHz, CDCl₃); δ -0.01(s, 3H), 0.035(s, 3H), 0.044(s, 3H), 0.05(s, 6H), 0.07(s, 3H), 0.84(s, 9H), 0.87(s, 18H), 1.16(m, 1H), 1.26-1.45(m, 3H), 1.32(s, 3H), 1.36(s, 3H), 1.40(s, 3H), 1.41(s, 3H), 1.46-1.55(m, 4H), 1.64(dd, J=6.0 and 14.4 Hz, 1H), 1.70-1.82(m, 4H), 1.90(br d, J=14.4 Hz, 1H), 2.21(dd, J=4.8 and 13.6 Hz, 1H), 2.32(t, J=10.2 Hz, 1H), 3.08(s, 3H), 3.40(m, 1H), 3.46-3.62(m, 3H), 3.66-3.86(m, 4H), 3.92(m, 1H), 4.03(m, 1H), 4.29(dt, J=4.8 and 10.2 Hz, 1H), 4.50(ABq, J_{AB}=12.3 Hz, 2H), 7.31(m, 5H), -10.0(br, 1H).

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