ORGANIC LETTERS
2003
Vol. 5, No. 7
1031−1034

Facile Oxidation of Aldehydes to Acids and Esters with Oxone

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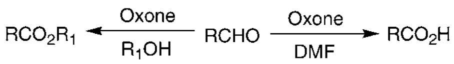
Received January 3, 2003

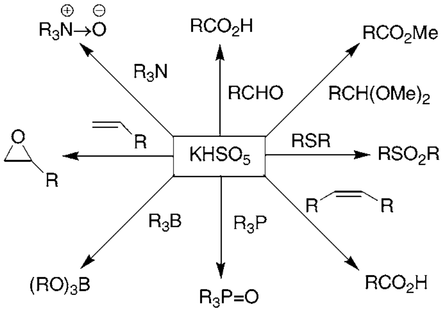
ABSTRACT


$$RCO_2R_1 \xleftarrow[R_1OH]{\text{Oxone}} RCHO \xrightarrow[\text{DMF}]{\text{Oxone}} RCO_2H$$

A highly efficient, mild, and simple protocol is presented for the oxidation of aldehydes to carboxylic acids utilizing Oxone as the sole oxidant. Direct conversion of aldehydes in alcoholic solvents to their corresponding ester products is also reported. These reactions may prove to be valuable alternatives to traditional metal-mediated oxidations.

Oxone, a potassium triple salt containing potassium peroxymonosulfate, is an effective oxidant for numerous transformations. For instance, Oxone is well-known for its oxidations of boron-, nitrogen-, phosphorus-, and sulfur-containing compounds and is also widely used to prepare dimethyldioxirane (DMDO) in buffered acetone, which subsequently epoxidizes olefins (Scheme 1).[1−10] Oxone's utility has also been demonstrated in oxidative cyclization and cleavage of olefins.[11−13] The use of Oxone as an efficient and mild oxidant has grown rapidly. This is due in part to Oxone's stability, ease of transport, nontoxic nature, nonpolluting byproducts, and cost-effectiveness.

Scheme 1



Previously, it has been demonstrated that Oxone or DMDO can affect the oxidation of simple aromatic aldehydes to their corresponding carboxylic acids using aqueous acetone- or aqueous acetonitrile-based systems.[14−16] Webb and co-workers have attributed the oxidative activity to Oxone itself while Baumstark and co-workers demonstrate that their DMDO oxidation proceeds through a radical-based mechanism. However, Oxone has not been studied and utilized extensively as a potentially routine reagent for the oxidation of aldehydes to carboxylic acids or its derivatives, which typically utilize transition-metal oxidants or bleach.[17−19]

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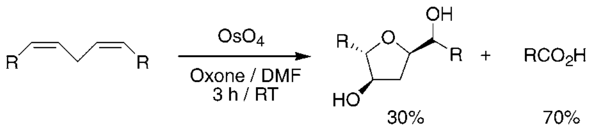
10.1021/ol0340078 CCC: $25.00

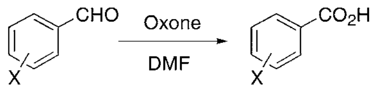
Our interest in this area was piqued during our investigation of the oxidative cyclization of 1,4-dienes. In the course of this study, we observed significant amounts of overoxidation that gave rise to carboxylic acids as the major byproducts (Scheme 2).[12] This led to studies on the oxidative cleavage of olefins, where although clean conversion to aldehydes as the immediate oxidation products was observed, the isolable products were carboxylic acids.[11] We have now pursued the optimization of this aldehyde oxidation to carboxylic acids and in the process have also discovered a new route for the direct conversion of aldehydes to esters. The scope and limitations for these oxidative processes are presented. The present method is attractive, since as opposed to most methodologies that utilize Cr, Mn, Ru, or other transition-metal oxides, the environmentally benign reagent Oxone mediates these highly efficient oxidations.[1,2,13]

Scheme 2



Initially, oxidation of aryl aldehydes to carboxylic acids with Oxone in DMF were investigated, the results of which are summarized in Table 1. In most cases, the desired carboxylic acids were obtained in >85% yield. Electron-withdrawing and electron-neutral benzaldehydes were oxidized efficiently (Table 1, entries 1−7). Halogenated benzaldehydes were also oxidized effortlessly to their corresponding halogenated benzoic acids in good yields (Table 1, entries 8−10). However, electron-rich substrates such as 4-hydroxybenzaldehyde and *p*-anisaldehyde (Table 1, entries 12 and 13) provided the formate esters **14** and **15** as the major products in 62% and 58% yield, respectively (Scheme 3). This is consistent with previous observations for the oxidation of electron-rich aromatic rings that are presumed to undergo a Baeyer−Villiger reaction where the phenolic or Dakin products were obtained (Scheme 3).[16] As expected, meta-substituted electron-donating groups do not yield substantial amounts of the Dakin product (Table 1, entry 11).

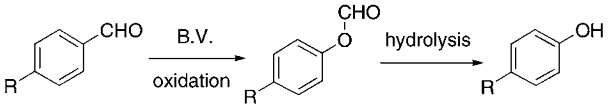
Table 1. Oxone Oxidations of Aromatic Aldehydes[a]



entry	X	product	yield[b] (%)
1	4-NO_2, **1**	**1a**	95
2	4-CN, **2**	**2a**	85
3	2-NO_2, **3**	**3a**	90
4	4-CO_2Me, **4**	**4a**	95
5	H, **5**	**5a**	97
6	4-Me, **6**	**6a**	97
7	3-NO_2, **7**	**7a**	95
8	2-Cl, **8**	**8a**	90
9	4-Cl, **9**	**9a**	97
10	3-Br, **10**	**10a**	97
11	3-OH, **11**	**11a**	63
12	4-OH, **12**	**12a**	19[c]
13	4-OMe, **13**	**13a**	31[d]

[a] Aldehyde (1 equiv), Oxone (1 equiv), DMF (0.2 *M*), 3 h, rt. [b] Isolated yields. [c] 62% yield of **14**. [d] 58% yield of **15**.

Scheme 3



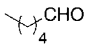
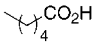
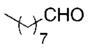
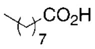
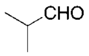
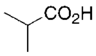
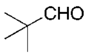
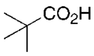
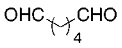
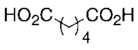
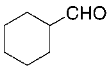
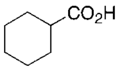
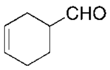
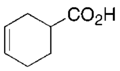
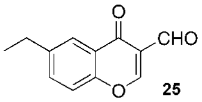
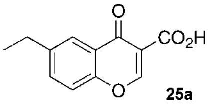
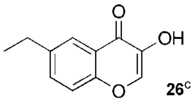
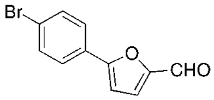
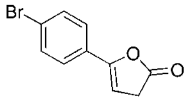
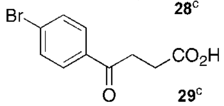
12, R = OH
13, R = OMe
14, R = OH
15, R = OMe
16, R = OH
17, R = OMe

The potential scope of this method was evident when the protocol was extended to simple aliphatic aldehydes (Table 2, entries 1−7). In most cases, the oxidation proceeds with high efficiency and yields of greater than 90% were obtained. While affording clean reactions (as evident by GC analysis), smaller aliphatic aldehydes (Table 2, entries 3 and 4) provided low yields due to problematic isolation from DMF. Olefinic aldehydes such as **24** were also oxidized efficiently without any observable reactivity at the double bond functionality. Oxidation of the electron-rich aldehydes **25** and **27** again provided primarily the Dakin products (Table 2, entries 8 and 9). Interestingly, the oxidation of 5-(4-bromophenyl)furfural **27** leads to the 1,4-dicarbonyl system **29** through a simple oxidative process upon hydrolysis of the dehydrolactone **28** (>70% combined yield). The γ-keto carboxylic acid **29** was the sole isolated product (72% yield) when oxidation of **27** was followed by a basic workup.

A key feature of the oxidation protocol to carboxylic acids is its inherent simplicity. A mixture of the aldehyde (1 equiv) and Oxone (1 equiv) in DMF (0.1−1.0 M) is stirred for 3 h at rt. There is no need for rigorous exclusion of air or moisture in order to effect a clean oxidation; however, the reactions continue to work even with these added precautions. In most cases, a simple pass through a plug of silica is enough to obtain highly pure products.

Previous reports concerning the oxidation of aldehydes with Oxone were performed in aqueous acetone or acetonitrile. However, we have found that DMF is also effective for the oxidation and in some cases superior to aqueous conditions. To test the range of solvents that may promote this oxidation, a number of cyclic and linear hydrocarbons, ethers, esters, and amides were screened. Surprisingly, very few solvents provided the desired carboxylic acid product even after extended reaction times of up to 36 h. The absence of reactivity is not attributed to the lack of solubility of Oxone because a comparable study using a soluble peroxymonosulfate (n-Bu_4NHSO_5) provided similar results.[20] Interestingly, solvents such as NMP, HMPA, and pyrrolidinone were also as effective as DMF in the oxidation of benz-

Table 2 [a]

entry	substrate	product	yield (%)[b]
1	 **18**	 **18a**	97
2	 **19**	 **19a**	99
3	 **20**	 **20a**	33
4	 **21**	 **21a**	47
5	 **22**	 **22a**	84
6	 **23**	 **23a**	97
7	 **24**	 **24a**	93
8	 **25**	 **25a**	34
		 **26**[c]	52
9	 **27**	 **28**[c]	42
		 **29**[c]	30

[a] Aldehyde (1 equiv), Oxone (1 equiv), DMF (0.2 M), 3 h, rt. [b] Isolated yields. [c] **26**, **28**, and **29** represent Dakin products.

aldehyde with Oxone providing >96% yield of benzoic acid in all cases.

As a fortuitous extension of the solvent study, the oxidation of aldehydes with Oxone in alcoholic solvents cleanly provided high conversion to esters. Thus, the oxidation of benzaldehyde in methanol did not yield the expected carboxylic acid, but instead the methyl ester was obtained. The present strategy complements other known methods that directly convert aldehydes to esters such as oxidation in the presence of alcohol with Br_2 or I_2, NBS/AIBN, PDC, HCN/MnO_2, or performed electrochemically.[21−25] Additionally, we found that other alcohols such as ethanol, *n*-propanol, and 2-propanol also provide their corresponding esters in excellent yields, although oxidation in *tert*-butyl alcohol furnished the carboxylic acid as the sole product (Table 3, entries 1−9).

Table 3. Oxidation of Aldehydes to Esters[a]

entry	substrate	solvent	product	yield[b] (%)
1	**5**	MeOH	**5b**	96
2	**5**	EtOH	**5c**	90
3	**5**	*n*-PrOH	**5d**	94
4	**5**	*i*-PrOH	**5e**	95
5	**5**	*t*-BuOH	**5a**	98
6	**18**	MeOH	**18b**	93
7	**18**	EtOH	**18c**	95
8	**18**	*i*-PrOH	**18e**	90
9	**18**	*t*-BuOH	**18a**	98
10	**1**	MeOH	**1b**	98[c]
11	**2**	MeOH	**2b**	98[c]
12	**6**	MeOH	**6b**	94
13	**9**	MeOH	**9b**	98
14	**12**	MeOH	**12b**	9[d]
15	**13**	MeOH	**13b**	19[d]
16	**19**	MeOH	**19b**	92
17	**20**	MeOH	**20b**	91[e]
18	**21**	MeOH	**21b**	76[e]
19	**22**	MeOH	**22b**	98
20	**23**	MeOH	**23b**	83
21	**27**	MeOH	**30**[f]	75

[a] Aldehyde (1 equiv), Oxone (1 equiv), ROH (0.2 M), 18 h, rt. [b] Isolated yields. [c] These reactions were carried out at 50 °C for 18 h. [d] The phenol products **16** (77%) and **17** (77%) were isolated as the major products for entries 14 and 15. [e] GC yield. [f] Methyl ester of **29**.

It is important to note that the esters are not obtained as the result of the oxidation of aldehydes to carboxylic acids followed by Fischer-type esterification of the acids in alcoholic solvents. Incubation of benzoic acid in methanol with Oxone for a prolonged period did not result in the isolation of methyl benzoate, but in fact the starting acid was re-isolated quantitatively.

The direct oxidation of a variety of aryl and alkyl aldehydes to their corresponding methyl esters is also illustrated in Table 3 (entries 10−19). Oxidation of aryl aldehydes with electron-withdrawing substituents showed slow conversion to the esters (Table 3, entries 10 and 11) initially providing dimethyl acetals in addition to the ester products. This was overcome by heating the reactions to reflux overnight, which provided clean conversion to the desired methyl esters **1b** and **2b**. Oxidation of **6** and **9** (electroneutral aromatics aldehydes) and **19**−**23** (aliphatic aldehydes) proceeded smoothly at rt to furnish the desired methyl esters in excellent yields. In the case of electron-rich aromatic substrates, as with the oxidations to carboxylic acids in DMF, the Dakin products were observed. Thus, 4-hydroxybenzaldehyde, **12**, and *p*-anisaldehyde, **13**, provided primarily phenols **16** and **17** in 77% yield for both (Scheme 3), along with small amounts of the corresponding

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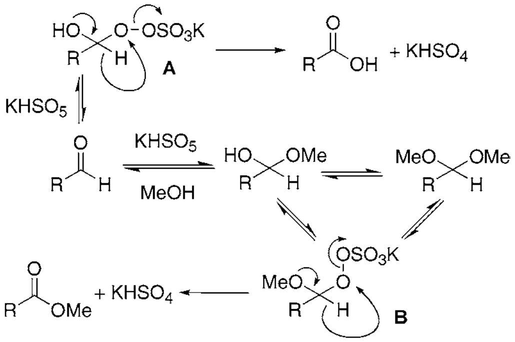
esters (Table 3, entries 14 and 15). Additionally, oxidation of **27** provided 75% yield of the γ-ketomethyl ester product **30** (methyl ester of **29**).

Noteworthy, is the fact that isopropyl esters are made with ease in high yields. However, as mentioned above, *tert*-butyl esters cannot be accessed, most probably due to the sterics of the bulky alcohol. Although at this time conversion of aldehydes to esters proceed best if the reaction is performed in the alcoholic solvent (in order to circumvent the formation of carboxylic acids), studies are underway with mixed solvents and show promising indications that the oxidation to carboxylic acids could be retarded in favor of esterification. Thus, it could be possible to lessen the amounts of alcohol used in the oxidation.

Although any mechanistic discussion is speculative at this point, we believe that the oxidation proceeds via a Baeyer–Villiger process. As depicted in Scheme 4, the proposed intermediates in the oxidation of aldehydes to carboxylic acids and esters are mixed peroxyacetals **A** and **B**. Rearrangement of intermediates **A** and **B** would yield the products by expelling bisulfate. Corroboration for the proposed mechanism is based on the well-understood oxidation of aldehydes to carboxylic acids with peroxyacids.[26] Also, recently it has been demonstrated that acetals are oxidized to their corresponding esters with Oxone,[10] and thus, intermediate **B** could be derived from either the hemiacetal or acetal (Scheme 4). It should be pointed out that Oxone is slightly acidic and, therefore, could catalyze the formation of the presumed peroxyacetals. Presently, mechanistic studies including use of ^{18}O-labeled aldehydes and NMR experiments to observe transient intermediates are underway.

Scheme 4



In conclusion, we have demonstrated a simple and effective one-pot protocol to oxidize aldehydes directly to acids or esters. These reactions are facile, high-yielding, and easy to work up (most do not require chromatography) and should provide a mild oxidative alternative for organic chemists. The mechanism of these transformations is being investigated and will be reported in due course.

Acknowledgment. Generous support was provided in part by Michigan State University Startup funds to B.B. and the Michigan Economic Development Corporation (GR-183). G.O.H. was supported in part by the McNair–SROP program (MSU).

Supporting Information Available: Detailed experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0340078

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