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Oxidation of Aldehydes with Oxone® in Aqueous Acetone

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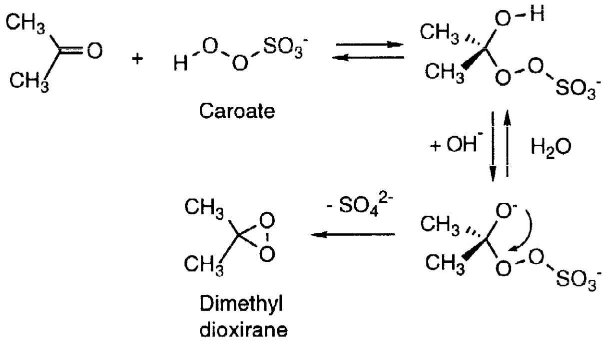
Abstract: Several aldehydes have been converted to the corresponding acids in good to excellent yields. The oxidant was Oxone® (potassium peroxymonosulfate), the reactions were performed in either 20% aqueous acetone, water, or aqueous acetonitrile, and buffered with sodium bicarbonate. © 1997 Elsevier Science Ltd. All rights reserved.

We continue to be interested in developing a general method for the oxidation of organic substrates with Oxone® in aqueous acetone within a narrow pH range (7 to 7.5). In this regard, we have already studied the oxidations of sulfides to sulfones or sulfoxides,[2] primary amines to nitro compounds,[3] and boronic esters or acids to alcohols.[4] During all of these investigations we observed a noticeable difference in reactivity of substrates towards oxidation by either the caroate(peroxymonosulfate) or caroate/acetone mixture. In the latter medium which is buffered to pH 7 - 7.5, dimethyldioxirane is presumed to be generated *in situ* under these reaction conditions (Scheme 1).[5]

Scheme 1



Baumstark[6] has demonstrated that dimethyldioxirane in acetone and in the absence of light oxidized substituted benzaldehydes to the corresponding benzoic acids; while Jiang[7] has reported the use of Oxone® in either anhydrous acetone or aqueous acetone as a means to oxidize aldehydes. Jiang's aqueous acetone method incorporates a sequential dosing of Oxone® followed by water (repeated four times). In this approach, the pH of the medium varies considerably; as the Oxone® is consumed, the reaction becomes acidic.[8]

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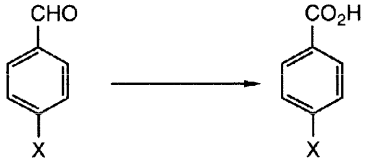
Subsequent charges of Oxone® increase the pH. A limitation of this methodology is that dimethyldioxirane is known to only form within a narrow pH range, with a limited life time outside of this neutral pH range.[5] Intrigued by these early studies, coupled with our interest in investigating the oxidation of organic substrates[2,3,4] with potassium peroxymonosulfate in medium known to favor dimethyldioxirane formation,[9] we initiated a study of aldehyde oxidations with Oxone® in 20% aqueous acetone, water, or aqueous acetonitrile within a narrow pH range (7 to 7.5).

Surprisingly in Jiang's study he never attributed the extent of reactivity he observed to merely the Oxone® acting as the oxidant verses that of the proposed dimethyldioxirane contribution. While Jiang's reactions were fairly quick (4 to 8 hours), Baumstark's reactions with neat dimethyldioxirane were reported to be more sluggish (18 hours). We were further intrigued by the fact that both studies reported the successful oxidation of *p*-anisaldehyde to produce *p*-anisic acid. We initiated a study of para-substituted benzaldehydes in order to assess any difference in reactivity of either Oxone® or *in situ* generated dimethyl dioxirane (Scheme 2). For the oxidation of *p*-nitrobenzaldehyde, benzaldehyde or *p*-bromobenzaldehyde we observed no difference in reactivity or yield when we performed the oxidations in the presence of acetone (Table 1). This suggests that Oxone® is responsible for the reactivity observed. To further support this hypothesis we were unable to produce significant amounts of *p*-anisic acid under our reaction conditions, instead the sole product, either in the presence or absence of acetone, was the Dakin product (*p*-methoxyphenol). By evaluating the crude reaction mixtures by HPLC we observed the formation of less than 1.0% (PAR) of *p*-anisic acid.

Scheme 2



X = NO_2, H, Br, CO_2CH_3, $COCH_3$

Table 1

X	Eq. Oxone®	Temp. and Time	Yield (%)
NO_2	0.9 eq.	20 to 25 °C, 1 Hr	89 [91][a]
H	2.7 eq.	20 to 25 °C, 1 Hr	71 [73]
Br	1.8 eq.	2 °C, 2 1/2 Hrs	88 [85]
CO_2CH_3	0.9 eq.	20 to 25 °C, 1 1/2 Hrs	90 [94]
$COCH_3$	0.9 eq.	20 to 25 °C, 1 Hr	90 [86]

a) Yields [ ] obtained when the reactions were performed in the absence of acetone.

Electron deficient aromatic rings appear to undergo this oxidation with greater ease than electron rich aromatic rings. In this regard we initiated a study of benzaldehydes substituted with one or more oxygen atoms delocalized in the aromatic π-system (Table 2). We were most interested in studying those substrates which are prone to produce the Dakin product from peroxide type reaction pathways. Only in the case of *m*-anisaldehyde were we able to produce the desired oxidation product, *m*-anisic acid, in modest yield. In the case of piperonal, *o*-hydroxy-, or *m*-methoxy- substituted benzaldehydes we observed only trace amounts[10] of the corresponding acids in the crude reaction mixtures. The majority of the starting material was converted to the Dakin product. Only in the cases of salicylaldehyde and *m*-anisaldehyde did we observe a rate enhancement when the reaction was performed in the presence of acetone.

Table 2

Aldehyde	Product	Eq. Oxone®	Temp. and Time	Yield (%)
m-Anisaldehyde	*m*-Anisic acid	3.6 eq.	20 to 25 °C, 1 Hr	69 [40]
p-Anisaldehyde	*p*-Methoxyphenol	2.7 eq.	2 °C, 1 Hr	58 [68]
Salicylaldehyde	Catechol	0.9 eq.	20 to 25 °C, 5 minutes	79 [37]
Piperonal	Sesamol	2.7 eq.	2 °C, 3 Hrs	54 [56]

This methodology was extended to include the oxidation of simple aliphatic aldehydes as well as those which contain functionality (Table 3). In this series we observed *a modest* increase in yield when the reactions were performed in the presence of acetone. The most dramatic effect of acetone was for the oxidation of phenylpropargyl aldehyde in which we obtained a 73% conversion to phenylpropiolic acid, versus only a 37% conversion in the absence of acetone. Thus, this mild and neutral oxidation protocol appears to allow for the selective oxidation of an aldehyde in the presence of an alkyne. In the case of linear aldehydes we observed that longer chain aldehydes were oxidized more efficiently than shorter chain aldehydes under our buffered conditions (pH 7 to 7.5). But more importantly we observed no significant difference in the oxidation rates in the presence or absence of acetone. Jiang[7] reported an opposite trend when the oxidation were performed in the absence of a buffer (sodium bicarbonate). Aldehydes substituted on a carbocylic ring also undergo this oxidation to produce the desired acids, and slightly higher yields were obtained upon the addition of acetone. Most surprising to us was our inability to oxidize *trans*-cinnamaldehyde to produce either *trans*-cinnamic acid or *trans*-β-phenylglycidic acid.[11] The only products isolated with or without acetone were benzoic acid and phenyl acetic acid.

In order to elucidate the possible mechanism for the formation of both benzoic acid and phenyl acetic acid we prepared an authentic sample of *trans*-β-phenylglycidic acid,[11] and subjected this material to our reaction conditions. Although we observed the disappearance of the *trans*-β-phenylglycidic acid, we did not observe the formation of any benzoic acid or phenyl acetic acid. The mechanism of this oxidative degradation of cinnamaldehydes under our reaction conditions still remains illusive (Scheme 3).

Scheme 3

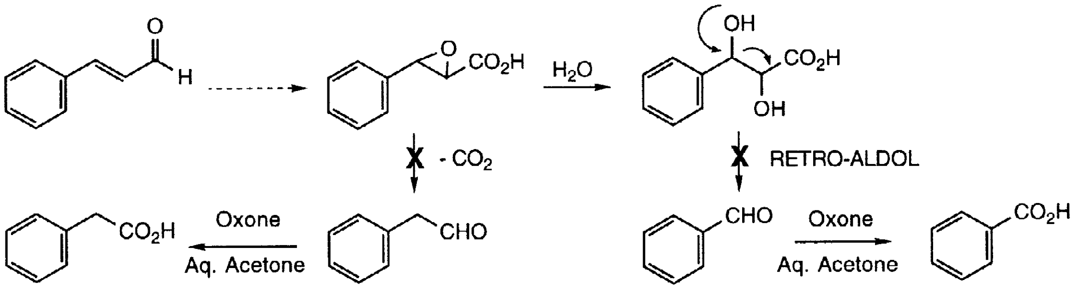


Table 3

Aldehyde	Product(s)	Eq. Oxone®	Temp and Time	Yield (%)
Phenylacetaldehyde	Phenylacetic acid	2.7 eq.	2 °C, 15 Hr	63 [54]
Butyraldehyde	Butyric acid	0.9 eq.	22 °C, 2.5 Hr	72 [70]
Nonyl aldehyde	Nonoic acid	1.8 eq.	22 °C, 1.5 Hr	86 [80]
Isovaleraldehyde	Isovaleric acid	1.8 eq.	22 °C, 1 Hr	72 [36]
Phenylpropargyl aldehyde	Phenylpropiolic acid	0.9 eq.	2 °C, 3.5 Hr	73 [37]
Cyclopropane-carboxaldehyde	Cyclopropane-carboxylic acid	1.8 eq.	22 °C, 3 Hr	71 [67]
Cyclohexyl-carboxaldehyde	Cyclohexyl-carboxylic acid	3.6 eq.	22 °C, 4 Hr	53 [32]
trans-Cinnamaldehyde	Phenylacetic acid	2.7 eq.	2 °C, 1Hr	40 [33]
	Benzoic acid			24 [25]

a) Yields [ ] obtained when the reactions were performed in the absence of acetone.

In summary, we have found that for the oxidation of electron-deficient aromatic rings there appears to be no advantage in performing these oxidations in the presence of acetone. For these substrates Oxone® buffered at pH 7-7.5 alone acts as a very efficient oxidant for this class of aldehydes. In the case of electron-rich aromatic rings which were either ortho-, meta-, or meta-para- substituted with oxygen atoms we were unable to form any appreciable amounts of the desired acids; instead the Dakin reaction is the major pathway. This observation is not consistent with dimethyldioxirane oxidations of aldehydes[6] or those results reported by Jiang.[7] The observation of the formation of Dakin products supports Oxone® acting as oxidant in these cases. In the case of aliphatic aldehydes there seems to be an advantage in performing these oxidations in aqueous acetone, although we are not quite sure of the extent that *in situ* generated dimethyldioxirane may contribute to the overall oxidation.

EXPERIMENTAL SECTION

General: ^{1}H NMR spectra were recorded on a Bruker AC 300 (300 MHz for ^{1}H) and chemical shifts were referenced to solvent peaks: δ 7.24 (residual $CHCl_3$) and δ 2.50 (residual DMSO). TLC analysis were conducted on 0.25 mm E. Merck precoated silica gel 60 F_{254}, and Merck silica gel 60 (particle size 0.040-0.063 mm) was used for column chromatography. HPLC analyses were performed on a Hewlett Packard 1050 Series using acetonitrile/water/TFA in various proportions as the mobile phase. GC analyses were performed on a Hewlett Packard 5890A gas chromatograph. Unless otherwise stated, materials were obtained from commercial suppliers and used without any further purification.

Preparation of *p*-Nitrobenzoic acid: To a 250 mL, three-necked, round bottom flask was added *p*-nitrobenzaldehyde (0.778 g, 5.15 mmol), acetonitrile (10 mL), water (15 mL), and sodium bicarbonate (3.50 g, 41.7 mmol). The mixture was stirred while acetone (5 mL) was added, followed by the dropwise addition of Oxone® (2.860 g, 4.65 mmol) in an aqueous EDTA solution (4 x 10^{-4} M, 18 mL). After stirring for 1 hour, the reaction was quenched with an aqueous sodium bisulfite solution (50% w/w, 9.0 g) and acidified with HCl (6N, 10 mL). The aqueous solution was cooled to 0 °C for two hours, vacuum filtered, and washed with ice cold water to afford *p*-nitrobenzoic acid (0.769 g, 89%) as white crystals, mp 234-237 °C. Anal. Calcd. for $C_7H_5NO_4$: C, 50.31; H, 3.02; N, 8.38. Found: C, 49.93; H, 2.88; N, 7.94. ^{1}H NMR (DMSO-d_6) δ 8.13-8.17 (d, J = 8.8 Hz, 2H), 8.29-8.32 (d, J = 8.9 Hz, 2H). *Preparation without acetone:* Experiment was performed as above except CH_3CN (10 mL) was added in place of acetone to dissolve the starting material.

Preparation of Benzoic acid: To a 100 mL, three-necked, round bottom flask was added benzaldehyde (0.553 g, 5.21 mmol), water (15 mL), and sodium bicarbonate (3.50 g, 41.7 mmol). The mixture was stirred while acetone (5 mL) was added, stirred for an additional 5 minutes, followed by the dropwise addition of Oxone® (8.551 g, 15.9 mmol) in an aqueous EDTA solution (4 x 10^{-4} M, 54 mL) over a 10 minute period. After stirring for 90 minutes, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 36.0 g), acidified with HCl (6N, 10 mL), and diluted with chloroform (25 mL). The mixture was transferred to a separatory funnel, the organic layer isolated, and the aqueous layer was re-extracted with chloroform (5 x 25 mL). The combined organic layers were washed with water (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford benzoic acid (0.451 g, 71%) as a white solid, mp 119-121 °C. Anal. Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.95. Found: C, 69.02; H, 4.80. ^{1}H NMR ($CDCl_3$) δ 7.45-7.50 (t, J = 7.5 Hz, 2H), 7.59-7.64 (t, J = 7.3 Hz, 1H), 8.10-8.13 (d, J = 7.5 Hz, 2H). *Preparation without acetone:* Experiment was performed as above except CH_3CN (10 mL) was added in place of acetone to dissolve the starting material.

Preparation of *p*-Bromobenzoic acid: To a 250 mL, three-necked, round bottom flask was added NaOH (0.364 g, 9.1 mmol), water (15 mL), and *p*-bromobenzaldehyde (0.958 g, 5.18 mmol). The mixture was stirred vigorously while cooled to 0 °C, treated with sodium bicarbonate (3.50 g, 41.7 mmol), acetone (5 mL), and followed by the dropwise addition of Oxone® (5.698 g, 9.27 mmol) in an aqueous EDTA solution (4 x 10^{-4} M, 30 mL) at a rate that kept the internal temperature below 2 °C. After stirring for 2.5 hours, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 18.0 g), acidified with HCl (6N, 10 mL), and diluted with ethyl acetate (50 mL). The mixture was transferred to a separatory funnel, the organic layer was isolated, and the aqueous layer was re-extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (1x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford *p*-bromobenzoic acid (0.994 g, 91%) as a white solid, mp 259-251 °C. Anal. Calcd. for $C_7H_5BrO_2$: C, 41.82; H, 2.51; Br, 39.75. Found: C, 41.81; H, 2.65; Br, 39.69. ^{1}H NMR (DMSO-d_6) δ 7.68-7.71 (d, J = 8.5 Hz, 2H), 7.83-7.86 (d, J = 8.5 Hz, 2H). *Preparation without acetone:* Experiment was performed as above except CH_3CN (10 mL) was added in place of acetone to dissolve the starting material.

Preparation of *m*-Anisic acid: To a 100 mL, three-necked, round bottom flask was added *m*-anisaldehyde (0.699 g, 5.13 mmol), acetonitrile (10 mL), water (15 mL), and sodium bicarbonate (3.50 g, 41.7 mmol). The mixture was vigorously stirred for 5 minutes at 0 °C, acetone (5 mL) was added, followed by the dropwise addition of Oxone® (11.407 g, 18.6 mmol) in an aqueous EDTA (4 x 10^{-4} M, 72 mL) solution at a rate that kept the internal temperature below 2 °C. After stirring for 90 minutes, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 36.0 g) and acidified with HCl (6N, 15 mL). The solution was transferred to a separatory funnel and extracted with chloroform (5 x 25 mL). The combined organic layers were separated, washed with water (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude *m*-anisic acid (0.541 g, 69%) as white crystals, mp 100-101 °C. A sample was recrystallized with water to produce an analytically pure sample. Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.22; H, 5.22. ^{1}H NMR ($CDCl_3$) δ 7.14-7.17 (dd, J = 8.3 Hz and J = 0.9 Hz, 1H), 7.35-7.40 (t, J = 8.0 Hz, 1H), 7.70-7.73 (dd, J = 7.8 Hz and J = 1.2 Hz, 1H). *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of Mono-methylterephthalate: To a 100 mL, three-necked, round bottom flask was added water (15 mL), sodium bicarbonate (3.0 g, 35.7 mmol), methyl-4-formylbenzoate (0.820 g, 5.00 mmol), acetonitrile (5 mL), and acetone (5 mL). The mixture was vigorously stirred for 5 minutes followed by the dropwise addition of Oxone® (2.790 g, 4.54 mmol) in an aqueous EDTA (4 x 10^{-4} M, 18 mL) solution. After stirring for 90 minutes, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 9.0 g), acidified with HCl (6N, 7 mL), and diluted with ethyl acetate (50 mL). The mixture was transferred to a separatory funnel and the organic layer was isolated. The aqueous layer was re-extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield a crude white solid. The product was purified *via* a plug of silica gel (1.20 g) with the eluting solvent being ethyl acetate (250 mL) to afford mono-methylterephthalate (0.806 g, 90%) as white crystals, mp 218-219 °C. Anal. Calcd. for $C_9H_6O_4$: C, 60.00; H, 4.48. Found: C, 59.99; H, 4.57. ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H), 8.05 (s, 4H). *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of *p*-Methoxyphenol: To a 100 mL, three-necked, round bottom flask was added *p*-methoxybenzaldehyde (0.705 g, 5.18 mmol), water (15 mL), sodium bicarbonate (3.50 g, 41.7 mmol), and acetone (5 mL). The mixture was vigorously stirred while cooled to 0 °C, followed by the dropwise addition of Oxone® (0.554 g, 13.9 mmol) in an aqueous EDTA (4 x 10^{-4} M, 50 mL) solution at a rate to keep the internal temperature below 2 °C. After stirring for 90 minutes the reaction was quenched with aqueous sodium bisulfite (50% w/w, 18.0 g). The aqueous medium was transferred to a separatory funnel and extracted with chloroform (3 x 50 mL). The combined organic layers were washed with water (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield a crude yellow solid. The product was isolated *via* column chromatography with the eluting solvent being ethyl acetate/cyclohexane (25/75) to afford *p*-methoxyphenol (0.374 g, 58%) as a white solid, mp 54-55 °C. Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.78; H, 6.46. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 6.76-6.77 (d, J = 1.6 Hz, 4H). *Preparation without acetone:* Experiment was performed as above except CH_3CN (5 mL) was added in place of acetone to dissolve the starting material.

Preparation of 4-Formylacetophenone: To a 250 mL round bottom flask was added 4-iodoacetophenone (13.34 g, 54.22 mmol), cuprous cyanide (5.34 g, 59.64 g), and DMF (130 mL). The flask was fitted with a condenser, heated to 150° C, and refluxed for 3 hours. The reaction was cooled to ambient temperature, filtered, transferred to a separatory funnel, diluted with water (350 mL), and extracted with tertbutylmethyl ether (3 x 300 mL). The combined organic layers were washed with 5% aqueous NH_4OH (1 x 100 mL) to remove copper salts, and washed with saturated brine (2 x 200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 4 -acetylbenzonitrile (6.84 g, 87%). The reduction with Raney® nickel was carried out according to T. van Es and B. Staskun[12] to afford 4-formylacetophenone.

Preparation of 4-Acetylbenzoic acid: To a 100 mL, three-necked, round bottom flask was added 4-formylacetophenone (0.7364 g, 4.97 mmol), acetone (5 mL), and water (15 mL). The solution was vigorously stirred, treated with sodium bicarbonate (3.50 g, 41.7 mmol), and followed by the dropwise addition of Oxone® (2.7608 g, 4.49 mmol) in an aqueous EDTA (4×10^{-4} M, 18 mL) solution. After one hour of stirring, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 9.0 g), acidified with HCl (6N, 7 mL), transferred to a separatory funnel, and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were extracted with 1% aqueous sodium carbonate (3 x 75 mL), the aqueous layer was isolated, acidified with HCl, and back-extracted with ethyl acetate (3 x 300 mL). The organic layer was isolated, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 4-acetylbenzoic acid (0.737 g, 90%) as a white solid, mp 206-207 °C. Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.78; H, 4.88. ^1H NMR (DMSO-d_6) δ 2.12 (s, 3H), 8.03 (s, 4H). *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of Catechol: To a 100 mL, three-necked, round bottom flask was added salicylaldehyde (0.629 g, 5.15 mmol), water (15 mL), sodium bicarbonate (3.50 g, 41.7 mmol), and acetone (5 mL). The mixture was vigorously stirred for 5 minutes, followed by the dropwise addition of Oxone® (2.857 g, 4.65 mmol) in an aqueous EDTA (4×10^{-4} M, 18 mL) solution. The reaction was stirred for 5 minutes, quenched with aqueous sodium bisulfite (50% w/w, 9.0 g), acidified with HCl (6N, 6 mL), and diluted with diethyl ether (50 mL). The mixture was transferred to a separatory funnel, the organic layer was isolated, and the aqueous layer was re-extracted with diethyl ether (5 x 50 mL). The combined organic layers were washed with saturated brine (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield a crude yellow solid. The product was isolated *via* column chromatography with the eluting solvent being ethyl acetate/hexanes (30/70) to afford catechol (0.445 g, 79%), mp 103-104 °C. Anal. Calcd. for $C_6H_6O_2$: C, 65.45; H, 5.49. Found: C, 65.46; H, 5.12. ^1H NMR (DMSO-d_6) δ 6.56-6.60 (m, J = 3.3 Hz, 2H), 6.67-6.72 (m, J = 3.3 Hz, 2H), 8.78 (s, 2H). *Preparation without acetone:* Experiment performed as above except CH_3CN (10 mL) was added in place of acetone to dissolve the starting material.

Preparation of Sesamol: To a 100 mL, three-necked, round bottom flask, was added piperonal (0.7528 g, 5.01 mmol), water (15 mL), acetonitrile (5 mL), sodium bicarbonate (4.0 g, 47.6 mmol), and acetone (5 mL). The solution was vigorously stirred, and treated with Oxone® (8.319 g, 13.5 mmol) in an aqueous EDTA (4×10^{-4} M, 54 mL) solution. After stirring for 1 hour the reaction was quenched with aqueous sodium bisulfite (18.0 g, 50% w/w), transferred to a separatory funnel, and extracted with ether (3 x 75 mL). The combined organic layers were washed with saturated brine (1 x 75 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a crude brown oil. The product was isolated *via* column chromatography using Florisil®, with the eluting solvent being ethyl acetate/hexanes (25/75) to yield sesamol

(0.3725 g, 54%) as a white solid, mp 62-63 °C. Anal. Calcd. for $C_7H_6O_3$: C, 60.87; H, 4.38. Found: C, 61.08; H, 4.13. ^{1}H NMR ($CDCl_3$) δ 5.90 (s, 2H), 6.22-6.25 (dd, J = 2.4 Hz and J = 8.1 Hz, 1H), 6.41-6.42 (d, J = 2.5 Hz, 1H), 6.62-6.65 (d, J = 8.3 Hz, 1H). *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of Phenylacetic acid: To a 100 mL, three-necked, round bottom flask was added phenylacetaldehyde (0.618 g, 5.15 mmol) and water (15 mL). The mixture was cooled to 0 °C and treated with sodium bicarbonate (3.50 g, 41.7 mmol), acetone (5 mL), and followed by the addition of Oxone® (8.549 g, 13.9 mmol) in an aqueous EDTA (4×10^{-4} M, 46 mL) solution at a rate to keep the internal temperature below 2 °C. After stirring for 15 hours, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 18.0 g) and acidified with HCl (6N, 10 mL). The solution was transferred to a separatory funnel and extracted with chloroform (5 x 50 mL). The combined organic layers were washed with water (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield a crude yellowish solid. The product was isolated *via* column chromatography with the eluting solvent being ethyl acetate/hexanes (50/50) to afford phenylacetic acid (0.442 g, 63%) as yellow crystals. A sample was recrystallized in petroleum ether to produce an analytically pure sample. Anal. Calcd. for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.95; H, 5.86. ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 2H), 7.26-7.32 (m, 5H). *Preparation without acetone:* Experiment performed as above except for the elimination of acetone.

Preparation of Butyric Acid: To a 1000 mL, three-necked, round bottom flask was added butyraldehyde (3.612 g, 50.1 mmol), water (150 mL), and acetone (50 mL). The solution was stirred vigorously while treated with sodium bicarbonate (35.0 g, 417 mmol) followed by the dropwise addition of Oxone® (27.612 g, 44.9 mmol) in an aqueous EDTA (4×10^{-4} M, 180 mL) solution over an one hour period. After stirring for 2.5 hours, the reaction was quenched with aqueous sodium bisulfite (90 g, 50% w/w) and acidified with HCl (70 mL, 6N). The solution was transferred to a separatory funnel and extracted with diethyl ether (3 x 300 mL). The combined organic layers were washed with saturated brine (1 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a clear oil. The product was isolated *via* vacuum distillation (bp 65 °C, 6-8 mm Hg) to afford butyric acid (3.185 g, 72%) as a clear liquid. ^{1}H NMR ($CDCl_3$) δ 0.94-0.99 (t, J = 7.4 Hz, 3H), 1.60-1.72 (m, J = 7.4 Hz, 2H), 2.30-2.35 (t, J = 7.4 Hz, 2H). MS (FAB) found: m/z 89. Calcd for $C_4H_9O_2$; MH^+, 89. *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of Nonanoic acid: To a 1000 mL, three-necked, round bottom flask was added nonanal (2.51 g, 17.6 mmol), acetone (17.5 mL), water (52.5 mL), and sodium bicarbonate (12.0 g, 143 mmol). The mixture was stirred for 10 minutes, followed by the addition of Oxone® (19.50 g, 31.7 mmol) in an aqueous EDTA (4×10^{-4} M, 126 mL) solution. After stirring for 90 minutes, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 54 g) and acidified with HCl (6N, 20 mL). The solution was transferred to a separatory funnel and extracted with chloroform (3 x 300 mL). The combined organic layers were washed with water (1 x 100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product as an oil. The product was isolated *via* high vacuum distillation (bp 110 °C, 15 mm Hg) to afford nonanoic acid

(2.14 g, 77%) as a clear liquid. ^{1}H NMR ($CDCl_3$) δ 0.84-0.89 (t, J = 7.2 Hz, 3H), 1.25-1.34 (m, 10H), 1.56-1.67 (m, J = 7.2 Hz, 2H), 2.30-2.36 (t, J = 7.5 Hz, 2H). MS (FAB) found: m/z 159. Calcd. for $C_9H_{19}O_2$; MH^+, 159. *Preparation without acetone:* Experiment was performed as above except CH_3CN (15 mL) was added in place of acetone to dissolve the starting material.

Preparation of Isovaleric Acid: To a 100 mL, round bottom, three-necked flask was added isovaleraldehyde (0.4405 g, 5.11 mmol), water (15 mL), and acetone (5 mL). The solution was vigorously stirred, sodium bicarbonate (3.50 g, 41.7 mmol) was added, followed by the dropwise addition of Oxone® (5.531 g, 9.00 mmol) in an aqueous EDTA (4×10^{-4} M, 36 mL) solution. After stirring for one hour, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 18.0 g) and acidified with HCl (6N, 10 mL). The solution was transferred to a separatory funnel and extracted with diethyl ether (3 x 40 mL). The combined organic layers were extracted with 1% aqueous sodium carbonate (3 x 60 mL). The combined base layers were acidified with HCl and back extracted with diethyl ether (3 x 70 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford isovaleric acid (0.3746 g, 72%) as a clear liquid. ^{1}H NMR ($CDCl_3$) δ 0.96-0.98 (d, J = 6.6 Hz, 6H), 2.05-2.16 (m, J = 4.8 Hz, 1H), 2.21-2.23 (d, J = 6.8 Hz, 2H). MS (FAB) found: m/z 103. Calcd. for $C_5H_{11}O_2$; MH^+, 103. *Preparation without aceotne:* Experiment was performed as above except for the elimination of acetone.

Preparation of Phenylpropiolic acid: To a 100 mL, three-necked, round bottom flask was added phenylpropargyl aldehyde (0.677 g, 5.20 mmol) and acetonitrile (15 mL). The solution was cooled to 0 °C, treated with sodium bicarbonate (3.50 g, 41.7 mmol), and acetone (5 mL). The mixture was vigorously stirred for 5 minutes followed by the dropwise addition of Oxone® (2.856 g, 4.66 mmol) in an aqueous EDTA (4×10^{-4} M, 15 mL) solution at a rate that kept the internal temperature below 2 °C. After stirring for 3.5 hours, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 9.0 g), acidified with HCl (6N, 7mL), and diluted with ethyl acetate (50 mL). The mixture was transferred to a separatory funnel, the organic layer was isolated, and the aqueous layer was re-extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated brine (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield a crude yellow solid. The product was isolated *via* column chromatography with the eluting solvent being cyclohexane/toluene/acetonitrile/acetic acid (40/40/20/4) to afford phenylpropiolic acid (0.760 g, 73%), mp 133-135 °C. Anal. Calcd. for $C_9H_6O_2$: C, 73.97; H, 4.14. Found: C, 73.75; H, 4.48. ^{1}H NMR ($CDCl_3$) δ 7.36-7.41 (t, J = 7.7 Hz, 2H), 7.45-7.50 (t, J = 7.3 Hz, 1H), 7.59-7.62 (d, J = 6.9 Hz, 2H). *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of Cylcopropanecarboxylic acid: To a 100 mL, round bottom, three-necked flask was added cyclopropane carboxaldehyde (0.3669 g, 5.23 mmol), water (15 mL), and acetone (5 mL). The solution was vigorously stirred while treated with sodium bicarbonate (3.50 g, 41.7 mmol) followed by the dropwise addition of Oxone® (5.547 g, 9.02 mmol) in an aqueous EDTA (4×10^{-4} M, 36 mL) solution. After stirring for 3 hours, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 9.0 g) and acidified with HCl (6N, 7 mL). The solution was transferred to a separatory funnel and extracted with diethyl ether (3 x 50 mL). The combined organic layers were extracted with 1% aqueous sodium carbonate (4 x 50 mL). The combined base extracts were acidified with HCl, and back extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with saturated brine (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford cyclopropanecarboxylic acid (0.3181 g, 71%) as a clear liquid. ^{1}H NMR ($CDCl_3$) δ 0.88-1.00 (m, 2H), 1.03-1.08 (m, 2H), 1.55-1.63 (m, 1H). MS (FAB) found: m/z 87. Calcd. for $C_4H_7O_2$; MH^+, 87. *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

Preparation of Cyclohexyl carboxylic acid: To a 1000 mL, three-necked, round bottom flask was added cyclohexanecarboxaldehyde (5.08 g, 45.3 mmol), water (150 mL), and acetone (50 mL). The solution was stirred vigorously, treated with sodium bicarbonate (30.82 g, 0.367 mol), and followed by the dropwise addition of Oxone® (100.45 g, 0.163 mol) in an aqueous EDTA (4 x 10^{-4} M, 600 mL) solution. After stirring for 4 hours, the reaction was quenched with aqueous sodium bisulfite (50% w/w, 90 g) and acidified with HCl (6N, 70 mL). The solution was transferred to a separatory funnel and extracted with ethyl acetate (3 x 0.9 L). The combined organic layers were washed with saturated brine (1 x 650 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product as a clear oil. The product was isolated *via* high vacuum distillation (bp 80 °C, 15 mm Hg) to afford cyclohexyl carboxylic acid (3.07 g, 53%) as a clear solid, mp 27-29 °C. ^{1}H NMR ($CDCl_3$) δ 1.21-1.33 (m, 3H), 1.37-1.49 (m, 2H), 1.61-1.65 (m, 1H), 1.71-1.78 (m, 2H), 1.90-1.94 (dd, J = 12.6 Hz and J = 2.0 Hz, 2H), 2.28-2.35 (m, 1H). MS (FAB) found: m/z 129. Calcd for $C_7H_{13}O_2$; MH^+, 129. *Preparation without acetone:* Experiment was performed as above except for the elimination of acetone.

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