ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Liquid-Liquid Extraction Protocol for the Removal of Aldehydes and Highly Reactive Ketones from Mixtures

Maria Marsian Boucher, Maxwell Hyland Furigay, Phong Kim Quach, and Cheyenne S. Brindle

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00231 • Publication Date (Web): 12 Jul 2017

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Liquid-Liquid Extraction Protocol for the Removal of Aldehydes and Highly Reactive Ketones from Mixtures

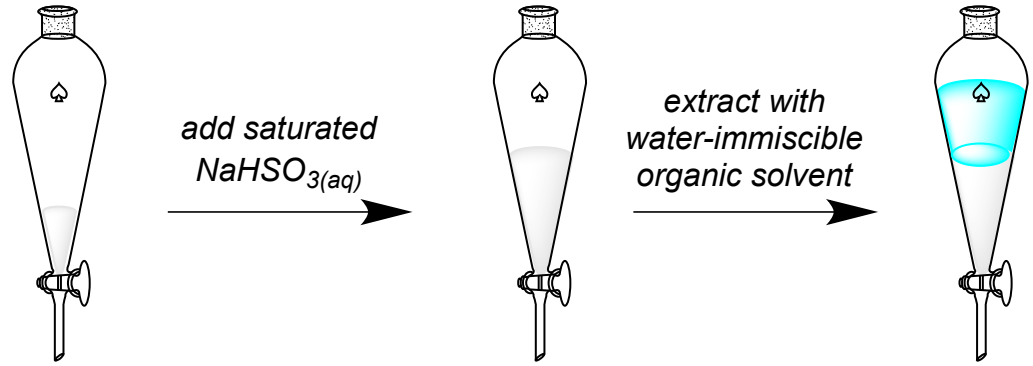
Maria M. Boucher, Maxwell H. Furigay, Phong K. Quach, and Cheyenne S. Brindle*

Trinity College, 300 Summit Street, Hartford, CT 06106

cheyenne.brindle@trincoll.edu

TOC graphic

remove aldehyde contaminants using a simple extraction protocol



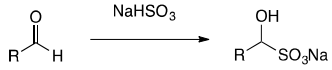
dissolve mixture in water-miscible organic solvent

Abstract
The reaction of bisulfite ion with aldehydes to form charged bisulfite adducts is a well-established method for the purification of aldehydes. This reaction has been modified to create a convenient liquid-liquid extraction method for the removal of aldehydes from mixtures. The use of a water-miscible solvent allows the reaction to occur during a simple 30 second shaking protocol by increasing the contact between the bisulfite ion and the aldehyde. Introduction of an immiscible solvent allows for extraction of the uncharged organic components away from the bisulfite adduct. The developed protocol is applicable to a wide range of aldehydes, including sterically-hindered neopentyl aldehydes. Sterically unhindered cyclic and linear ketones, as well as highly electrophilic ketones are also removed using this protocol. The mild conditions tolerate a wide range of functional groups, allowing for excellent aldehyde contaminant removal rates with high levels of recovery of the desired component.

Keywords
extraction, bisulfite, aldehyde, purification

Introduction

The ability to separate chemical components from mixtures of compounds is critical to the chemical field, including practicing organic chemists.[1] Numerous techniques are available for separation, yet difficulties in molecular separations remain an everyday issue. Recently, we encountered a particularly difficult separation that involved excess aldehyde that was used as a reagent in the synthesis of a desired product. This problem led us to investigate the use of an extraction protocol based on the reactivity of aldehydes with sodium bisulfite (equation 1). Extraction is a routine part of most chemical reactions, and a new protocol that could remove unwanted aldehydes from mixtures would provide a convenient tool for purification. Aldehydes are a particularly important functional group for synthesis due to their high reactivity, so this protocol would have widespread applicability. The results of these efforts, described herein, have produced a simple new protocol that we believe will be of great utility to synthetic chemists.



Equation 1.

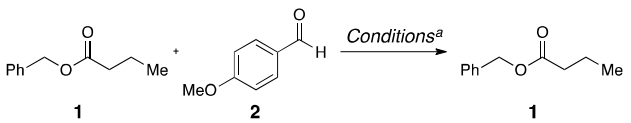
The reaction of sodium sulfite with aldehydes to form charged bisulfite adducts is a well-known reaction,[2,3] but its utility in the lab is mainly centered on its use in purifying aldehydes from mixtures, rather than removing them.[4,5] Outside of the lab, there are numerous commercial uses of bisulfite removal of aldehydes in a variety of settings.[6,7] In principle, using this reaction to remove aldehydes rather than purify them is merely a matter of nomenclature. In practice, however, this change required some manipulation to perform as a simple liquid-liquid extraction (LLE) procedure to achieve separation as a work-up, rather than using a more typical reaction setup. For an extraction to be successful with a simple shaking protocol, the rate of the reaction must be very fast. In general, this limits the types of reactions that can be achieved in extraction to reactions such as acid/base chemistry (e.g. sodium hydroxide), redox reactions (e.g. sodium thiosulfate), or the complexation of metals and ligands (e.g. copper sulfate), unless longer time periods are used for mixing (e.g. Rochelle's salt). The mechanism of

bisulfite addition is generally believed to occur through nucleophilic attack of the carbonyl by the sulfur of the bisulfite ion,[8] or of the sulfite dianion,[9] although a pericyclic mechanism has also been suggested to account for the high negative entropy measured for certain aldehydes.[10,11] If bisulfite addition to aldehydes is sufficiently rapid, a liquid-liquid extraction would be possible.

Results and Discussion

To model a typical to relatively challenging separation scenario, a contaminant aldehyde and model substrate were mixed in a 1:1 mole ratio, and several extraction protocols were evaluated. This mixing ratio was convenient for accurate determination of the decontamination factor using ^{1}H NMR integration analysis. Anisaldehyde was chosen as a model substrate because of its relatively low volatility, allowing for easy re-isolation and evaluation of different protocols. We also wanted an electron-rich aromatic ring that would not overly bias the system toward nucleophilic attack at the aldehyde. Benzyl butyrate was chosen as a non-volatile model substrate for purification. This choice also highlights the known chemoselectivity of the bisulfite reaction in terms of carbonyl reactivity toward aldehydes and cyclic ketones as compared to other carbonyl-containing functional groups.

Our first effort at LLE separation illustrated the kinetic limitations of this separation method (Table 1, entry 1). Using a typical extraction protocol, in which a 1:1 mixture of anisaldehyde and benzyl butyrate were dissolved in ethyl ether and then washed three times with saturated sodium bisulfite, negligible separation was achieved. Dissolving the 1:1 mixture in dichloromethane and filtering through solid sodium bisulfite also had a negligible effect (entry 2). However, when the more polar solvent methanol was used to elute through a column of solid sodium bisulfite, the amount of aldehyde remaining dramatically decreased, likely due to better solvation of the bisulfite ion (entry 3). Though the bisulfite adduct was not detected by ^{1}H NMR, the mass balance indicated that benzyl butyrate and remaining aldehyde were not the only components present. This observation led us to conclude that deuterated chloroform-insoluble bisulfite adducts were present after filtration, and therefore we needed to combine the improved solubility of bisulfite in polar organic solvents with the removal of the charged bisulfite adduct into an aqueous layer. Therefore, the 1:1 mixture was first dissolved in methanol, then saturated sodium bisulfite solution was added, and the single phase was shaken vigorously for approximately 30 seconds. At this point an immiscible solvent was introduced to provide two layers, which were then separated. Several solvent systems were evaluated for this extraction technique (entries 4-8), and all were found to remove 90% or more of the aldehyde from the model substrate. The best result was found for the nonpolar solvent hexanes (entry 8). Since many substrates are not soluble in pure hexanes, however, 10% ethyl acetate/hexane (entry 7) was chosen as a more general immiscible solvent for purification. It should be noted that ethyl acetate and ether, though not as effective, are still useful solvents for separation, allowing for the applicability of this protocol to more polar substrates that are not be soluble in 10% ethyl acetate/hexanes.



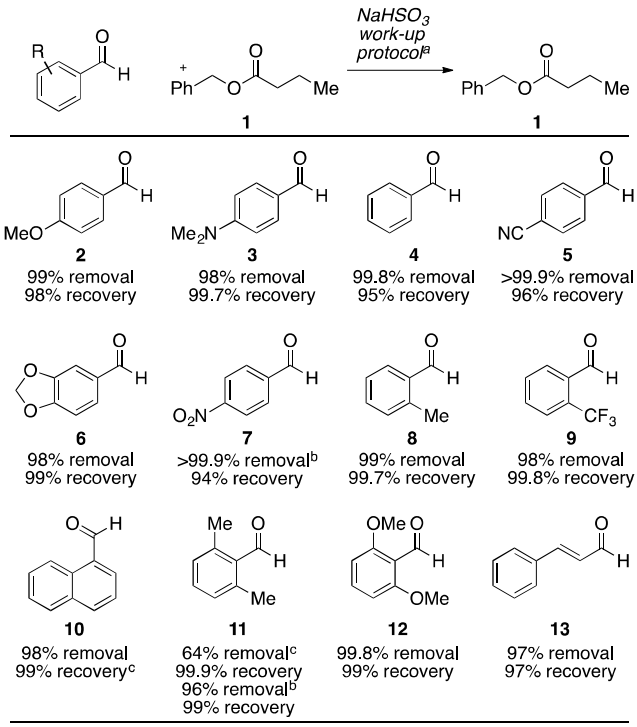
1 2 1

Entry	Conditions	DF[b]	Removal[c]
1	3 washes with saturated aq. $NaHSO_3$	1.6	37%
2	filtration through $NaHSO_{3(s)}$ with DCM	1.0	4%
3	filtration through $NaHSO_{3(s)}$ with MeOH	6.7	85%
4	1-phase MeOH/$NaHSO_3$, extract with Et_2O	10	90%
5	1-phase MeOH/$NaHSO_3$, extract with DCM	14	93%
6	1-phase MeOH/$NaHSO_3$, extract with EA	20	95%
7	1-phase MeOH/$NaHSO_3$, extract with 10%EA/hex	110	99.1%
8	1-phase MeOH/$NaHSO_3$, extract with hex	140	99.3%

Table 1. Separation of anisaldehyde from benzyl butyrate using sodium bisulfite. [a]A mixture of benzyl butyrate (250 µL, 1.4 mmol) and anisaldehyde (175 µL, 1.4 mmol) were tested using the listed conditions. [b]Decontamination factor. [c]Determined by ^{1}H NMR analysis. hex = hexanes.

With these promising results, we next began to examine the substrate scope of our extraction protocol with respect to the removable aldehyde component (Scheme 1). Aromatic aldehydes were easily removed. Electron-rich aldehydes, in addition to anisaldehyde **2**, such as *p*-dimethylaminobenzaldehyde **3** and piperonal **4** also were removed in high selectivity. Electron-neutral benzaldehyde **5**, and more electrophilic aldehydes, *p*-cyanobenzaldehyde **6** and *p*-nitrobenzaldehyde **7** were also removed effectively. The method was altered slightly for *p*-nitrobenzaldehyde **7**, due to insolubility of this substrate in methanol. Simply exchanging dimethylformamide for methanol as the miscible solvent proved effective, though this substitution required additional water washes to remove the less volatile solvent from the model substrate, which was not necessary with the more aqueous-soluble methanol. More sterically hindered *ortho*-substituted substrates 2-tolylaldehyde **8** and 2-trifluoromethylbenzaldehyde **9** were also easily removed. 1-Naphthaldehyde **10** required filtration through celite after treatment with saturated sodium bisulfite solution to effectively separate the water- and organic-insoluble bisulfite adduct from the organic layer. 2,6-Dimethylbenzaldehyde **11** was much less susceptible to the work-up protocol, giving only 64% removal. This substrate also required celite filtration. In contrast, 2,6-dimethoxybenzaldehyde **12** was almost completely removed under the separation conditions. α,β–Unsaturated aldehyde *trans*-cinnamaldehyde **13** was also effectively removed using this protocol.

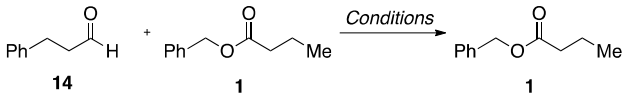
Scheme 1. Removal of aromatic aldehydes from benzyl butyrate.



[a]Benzyl butyrate (250 µL, 1.4 mmol) and aldehyde (1.4 mmol) were dissolved in 5 mL MeOH, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. [b]DMF instead of MeOH used. Organic layer washed two times with 15 mL water. [c]Required filtration to remove solid bisulfite adduct.

Non-aromatic aldehydes were found to be less effectively removed using this protocol, prompting us to further examine the extraction parameters using 3-phenylpropionaldehyde **14** as the model aliphatic aldehyde (Table 2). The standard work-up protocol used for aromatic aldehydes gave only 85% removal (entry 1). As expected from the results with anisaldehyde **2**, switching to the more non-polar extraction solvent hexane increased separation (entry 2). Performing the work-up a second time on the mixture isolated after one round of extraction gave 95% separation, but this is not ideal in terms of the ease and duration of the extraction protocol (entry 3). Similarly, stirring the mixture for 30 minutes, rather than using a simple shaking protocol, increased the separation to 98% (entry 4). In our initial protocol, we had diluted the aqueous layer before extracting with an immiscible solvent to improve the bisulfite adduct solubility in the aqueous layer and improve separation. This dilution could push the equilibrium away from bisulfite adduct formation, therefore we attempted omitting the dilution step (entry 5). This change resulted in only 75% removal of aldehyde **14**. Increasing the amount of the miscible solvent by a factor of two increased the separation to 93% (entry 6). Switching to potassium bisulfite gave poorer results when compared to the sodium salt (entry 6 vs. entry 7). Switching to the more nucleophilic sulfite dianion[10] also gave poorer results (entry 8). Mechanistic evidence suggests that this aldehyde addition, though faster than bisulfite addition, does not favor the dianionic adduct that is formed, making this pathway to the final adduct a minor contributor to the overall mechanistic picture.[10,11] This conclusion is supported by our experimental observation. We decided to pursue increasing the miscible solvent volume

by a factor of two (entry 6) for our extraction protocol with non-aromatic aldehydes as the optimal balance of user ease and aldehyde removal, though it should be noted that increased mixing time gives the highest removal rates if purity is the main concern of the user.

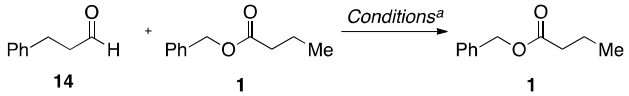


Entry	Modifications to standard procedure[a]	DF[b]	Removal[c]
1	NA	6.7	85%
2	hexane extraction	13	92%
3	repeat workup	20	95%
4	30 min stir with saturated $NaHSO_{3(aq)}$	50	98%
5	no dilution	4.0	75%
6	increase MeOH two-fold	14	93%
7	increase MeOH two-fold, $KHSO_3$	6.2	84%
8	increase MeOH two-fold, Na_2SO_3	1.6	36%

Table 2. Removal of 3-phenylpropionaldehyde from benzyl butyrate. [a]Standard procedure: 3-phenylpropionaldehyde (190 µL, 1.4 mmol) and benzyl butyrate (250 µL, 1.4 mmol) were dissolved in 5 mL MeOH, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. [b]Decontamination factor. [c]Determined by ^1H NMR analysis.

To explore the scope of the workup protocol with respect to the identity of the miscible solvent, we undertook a solvent screen using 3-phenylpropionaldehyde **14** as the model impurity (Table 3). All miscible solvents tested gave useful separation (Entries 1-11). The concentration of the components in these mixtures is approximately 0.3M, which is similar, in terms of order of magnitude, to the concentrations used for many reactions. This indicates that when a solvent that is miscible with water is employed for a reaction, the solvent need not be removed before performing the bisulfite workup described herein. The reaction mixture can simply be added to a separatory funnel and then saturated sodium bisulfite can be added, shaken, and then an immiscible solvent can be added to extract the desired organic components away from the bisulfite adduct and other water soluble materials, including the solvent. The best result found in this screen was with acetone and dimethyl sulfoxide. The success of acetone was initially surprising, as the solvent contains a carbonyl that can competitively react with bisulfite ion. Indeed, a noticeable exotherm was observed, but despite this apparent reaction between bisulfite and the solvent, the removal rates were excellent, likely due to the higher rate of reaction caused by the exotherm. Interestingly, when the amount of acetone was increased two-fold as before (Table 2, entries 6-8) the material solidified upon addition of the bisulfite solution, presumably because the amount of heat generated was sufficient to cause large amounts of acetone to form a solid bisulfite adduct (entry 12). Thus, acetone was not used in subsequent workup protocols to avoid this unwanted solvent reactivity. Dimethyl sulfoxide also gave good separation results, but was accompanied by an unpleasant odor, presumably due to the formation of dimethyl sulfide under the mild

reducing conditions (entry 5). Although methanol gave inferior separation in comparison to other miscible solvents, its high water solubility and relatively low boiling point relative to the other miscible solvents screened makes it easy to remove from the purified substrate. For ease of use, this solvent is recommended, but if higher levels of aldehyde removal is required, dimethylformamide gives higher removal rates, particularly when a two fold increase is used, coupled with the use of hexanes as the immiscible solvent (entry 13). This is particularly useful for highly hydrophobic substrates that do not mix well with the aqueous layer, as the less polar dimethylformamide (relative to methanol) allows better mixing with the bisulfite-containing aqueous layer. The drawback to using this solvent is that an additional aqueous extraction is required to recover the substrate from the aqueous layer, and three additional water washes were required to deplete the dimethylformamide to undetectable levels by ^{1}H NMR. This extra washing was necessary due to dimethylformamide's less favorable partition coefficient between water and the immiscible organic solvent, and its lower volatility, relative to methanol.



14 **1** **1**

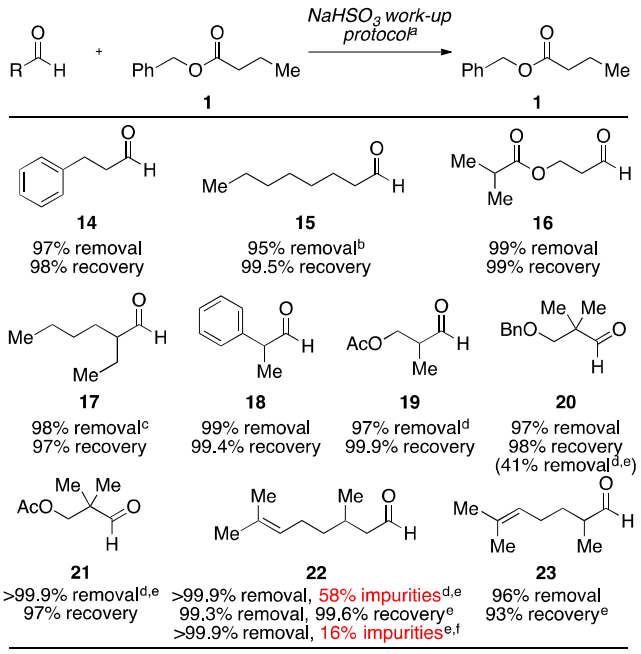
Entry	Solvent	DF[b]	Removal[c]	Entry	Solvent	DF[b]	Removal[c]
1	MeOH	6.7	85%	8	DMF	17	94%
2	EtOH	11	91%	9	MeCN	13	92%
3	*n*-PrOH	13	92%	10	DME	8.8	89%
4	*i*-PrOH	5.9	83%	11	acetone	20	95%
5	DMSO	20	95%	12	acetone[d]	NA	NA
6	THF	5.9	83%	13	DMF[d,e]	34	97%
7	1,4-dioxane	17	94%				

Table 3. Water-miscible solvent efficacy in the removal of 3-phenylpropionaldehyde from benzyl butyrate. [a]Standard procedure: 3-phenylpropionaldehyde (190 µL, 1.4 mmol) and benzyl butyrate (250 µL, 1.4 mmol) were dissolved in 5 mL solvent, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. [b]Decontamination factor. [c]Determined by ^{1}H NMR analysis. [d]10 mL solvent used. [e]Extracted with hexanes rather than 10% EA/hexanes.

Implementing the two-fold increase in the amount of the miscible solvent employed in the work-up protocol improved removal efficiency to above 95% for all aliphatic aldehydes tested (Scheme 2). For non-polar aldehydes, the more hydrophobic solvent dimethylformamide was used to give efficient separation. α-Unbranched aldehydes 3-phenylpropionaldehyde **14**, 1-octanal **15**, and 3-oxopropyl isobutyrate **16**[12,13] were all removed effectively, though celite filtration was necessary to remove the insoluble solid bisulfite adduct of 1-octanal **15**. Introducing branching adjacent to the aldehyde did not decrease efficiency of removal. 2-Ethylhexanal **17**, 2-phenylpropionaldehyde **18**, and 2-methyl-3-oxopropyl acetate **19**[14] were all removed with excellent efficiency. Increasing α-branching further was also well-tolerated. Neopentyl substrate **20**[15,16] demonstrates the difference in the standard protocol for aromatic versus aliphatic substrates in particularly dramatic fashion. When methanol is used, only 41%

removal is obtained, but by simply switching the identity of the miscible solvent to dimethylformamide, as well as doubling the volume of solvent used, 97% removal is achieved. For more polar substrates, such as acetate-protected neopentyl aldehyde **21**,[17] methanol is a suitable miscible solvent. This modification was also successful when applied to 2,6-dimethylbenzaldehyde **11**, resulting in an improvement from 64% removal to 96% removal (Scheme 1). Steric hindrance does not appear to be an important a factor in aldehyde separation under these conditions. Interestingly, the extraction protocol resulted in noticeable impurities when applied to a mixture of citronellal **22** with benzyl butyrate **1**. The mass balance after the workup protocol indicated that 58% of the original aldehyde mass remained after separation, though no aldehyde was observable by ^{1}H NMR. We suspected that the electron-rich alkene may be involved in a reaction with dissolved sulfur dioxide, which is well-known to isomerize alkenes.[18,19] Thin layer chromatography indicated that many different impurities had formed under these conditions. The solubility of sulfur dioxide in organic solvents is known to be low in hydrophobic solvents such as hexanes,[20–22] therefore the immiscible solvent used to extract benzyl butyrate was changed to hexanes to limit the interaction of citronellal **22** with sulfur dioxide. This small change eliminated the problem almost entirely, giving only a trace amount of impurity after the workup protocol. Hexanes are not capable of solvating many organic compounds, due to low polarity, so more polar alternatives to hexanes that would also limit alkene reactivity were explored. Chloroform, which is also known to have low sulfur dioxide solubility (though higher than hexane), may be a preferable solvent in many situations, given its higher polarity and dielectric constant. When chloroform was used as the immiscible extraction solvent, impurities were reduced as compared to the use of 10% ethyl acetate/hexanes, but they were still observable: 16% of the original aldehyde mass was retained after the protocol. Implementing the low sulfur dioxide extraction solvent hexane allowed for excellent results with alkene-containing aldehyde **23**, which was removed in 96% from benzyl butyrate, with no discernable impurities from the aldehyde by ^{1}H NMR or mass. In all cases, benzyl butyrate was recovered in 93% or greater yield using the dimethylformamide protocol.

Scheme 2. Removal of aliphatic aldehydes from benzyl butyrate.

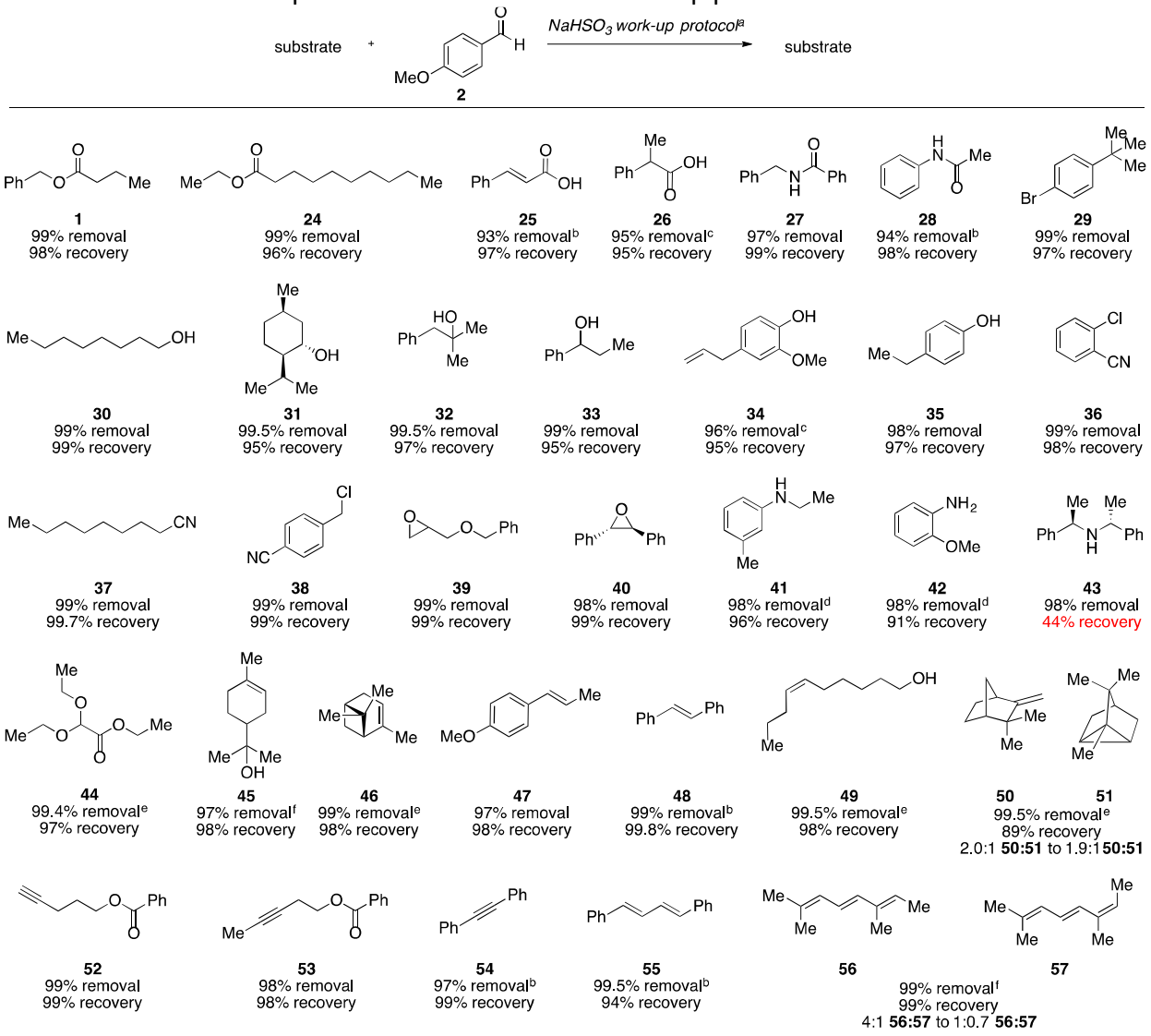


[a]Aldehyde (1.4 mmol) and benzyl butyrate (250 µL, 1.4 mmol) were dissolved in 10 mL DMF, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL hexanes. The aqueous layer was extracted once with hexanes and the combined organics were washed three times with water to remove DMF (25 mL, 10 mL, 5 mL). [b]Required filtration to remove solid bisulfite adduct. [c]Pentane used in place of hexanes. [d]10% EA/hexanes used in place of hexanes. [e] MeOH used in place of DMF. [f]$CHCl_3$ used in place of hexanes.

The substrate scope of this workup protocol was investigated, using anisaldehyde as a model contaminant (Scheme 3). A wide range of functional groups were found to be compatible with the protocol, including a variety of carbonyl compounds. Esters, carboxylic acids, and amides all gave excellent results (**1**, **24**-**28**). Aryl bromide **29** was also well-tolerated. Primary, secondary, tertiary and benzylic alcohols (substrates **30**-**33**), phenols (substrates **34** and **35**), and nitriles (substrates **36**-**38**) were all compatible with the work-up protocol as well. The procedure was also compatible with electrophilic substrates, such as benzyl chloride **38** and epoxides (substrates **39**[23] and **40**). Anilines **41** and **42** were also compatible with the protocol, though additional extraction of the aqueous layer was required to recover these more polar substrates. The protocol is not appropriate for more basic amines, such as secondary amine **43**, due to unwanted acid-base chemistry with the weakly acidic bisulfite ion (pKa 7.2). The mild work-up protocol is compatible with acid-sensitive functional groups such as acetal **44**. The use of electron-rich alkenes, such as α-terpineol **45** and α-pinene **46**, resulted in the observation of significant decomposition, in agreement with the results obtained for the removal of citronellal, though the decomposition in the case of α-pinene **46** was greater, presumably due to the presence of the reactive cyclobutane ring that is known to undergo ring-opening under a variety of conditions. Using hexane as the immiscible solvent resolved this issue, allowing for 98% re-isolation of both α-terpineol **45** and α-pinene **46**. The use of hexanes was not necessary for the disubstituted double-bond-containing substrates **47**-**50**, as these substrates did not

undergo degradation under the standard work-up conditions. Camphene **50** was subjected to the conditions as a 2:1 ratio together with tricyclene **51**. Very little change was observed in the ratio of the two isomers after the work-up protocol. Terminal alkyne **52**,[24] as well as internal alkynes **53**[25] and **54** did not undergo isomerization, even without the use of hexane to limit the solubility of sulfur dioxide. Diene **55** also did not undergo isomerization, however allo-ocimene **56** isomerized from a 4:1 mixture of trienes **56** and **57** to a 1:0.7 mixture after the bisulfite work-up,[26] even when hexanes was employed as the immiscible solvent. The substrate scope was found to be extremely broad using the mild conditions of the bisulfite work-up, making this method applicable for routine removal of aldehyde impurities from most organic reactions.

Scheme 3. Substrate scope of the sodium bisulfite work-up protocol.

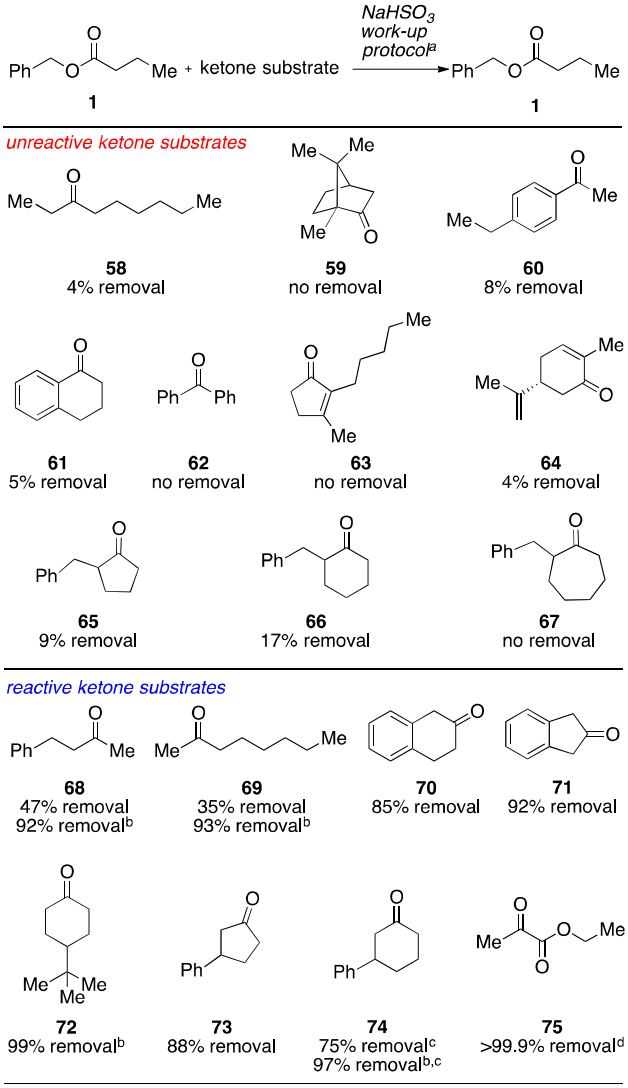


[a]Substrate (1.4 mmol) and anisaldehyde (175 µL, 1.4 mmol) were dissolved in 5 mL MeOH, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. [b]DMF used in place of MeOH. EA used in place of 10% EA/hex. The aqueous layer was extracted twice. The organic layer was washed three times with

water. [c]50% EA/hex used in place of 10% EA/hex. [d]The aqueous layer was extracted three times. [e]Pentane was used in place of 10% EA/hexanes. [f]Hexanes was used in place of 10% EA/hexanes.

With the compatibility of a wide-range of functional groups now established, we turned our attention to the reactivity of ketones, to see if these substrates would participate in the reaction with bisulfite on the time scale of the work-up protocol. Cyclic ketones are well-known to form bisulfite adducts,[27] so we were curious about which ketones would react under the work-up conditions, and which would remain unreacted. A variety of ketones were mixed with benzyl butyrate and the extent of their removal from this mixture was evaluated after the standard bisulfite work-up protocol using methanol as the miscible solvent. 3-nonanone **58** was only slightly depleted after the work-up, despite the minimal level of steric hindrance present for this linear ketone. The more sterically-hindered substrate camphor **59**, was not measurably removed from the mixture. Aromatic substrate 4'-ethylacetophenone **60** was largely retained in the mixture, as was α-tetralone **61** and benzophenone **62.** α,β-Unsaturated dihydrojasmone **63** and carvone **64** were also largely retained. This is notable, as 1,4-addition of bisulfite has been observed for carvone and other α,β-unsaturated ketones previously.[28] The rate of this conjugate addition must be slow relative to the timescale of the extraction protocol. Cyclic ketones with α-substituents **65**-**67**[29–33] were largely retained, although the six-membered ring substrate was removed by 19% from the mixture. Interestingly, non-aromatic methyl ketones benzyl acetone **68** and 2-octanone **69** were removed in 47% and 35%, respectively. The decrease in steric size from ethyl to methyl appears to increase bisulfite reactivity, as seen in the difference in removal rate (4% versus 35%) between ethyl ketone **58** and methyl ketone **69**. The rate of removal was enhanced to 92% and 93%, respectively, by using the DMF conditions developed for hydrophobic substrates. Cyclic unhindered substrates were found to be reactive under the conditions. β-tetralone **70,** 2-indanone **71**, 4-tert-butylcyclohexanone **72**, 3-phenylcyclopentanone **73**,[34,35] and 3-phenylcyclohexanone **74**[34,35] were all effectively removed. Filtration was required for nonpolar substrates **72** and **74**, which formed water and organic-insoluble bisulfite adducts. As observed with other nonpolar substrates, the removal of 3-phenylcyclohexanone **74** was greatly improved when dimethylformamide was employed as the miscible solvent (97% removal). α-Keto esters are known to be highly electrophilic, and therefore the complete removal of ethyl pyruvate **75** was unsurprising. In general, the ketones tested fell into two distinct groups: unreactive ketones (conjugated or slightly sterically hindered ketones: **58**-**67**) and reactive ketones (unhindered cyclic ketones, methyl acyclic ketones, and highly electrophilic ketones: **68**-**75**). This sharp distinction will prove convenient for routine separation of bisulfite-reactive carbonyl compounds from those carbonyl compounds that are unreactive.

Scheme 4. Ketone removal from a 1:1 mixture with benzyl butyrate.

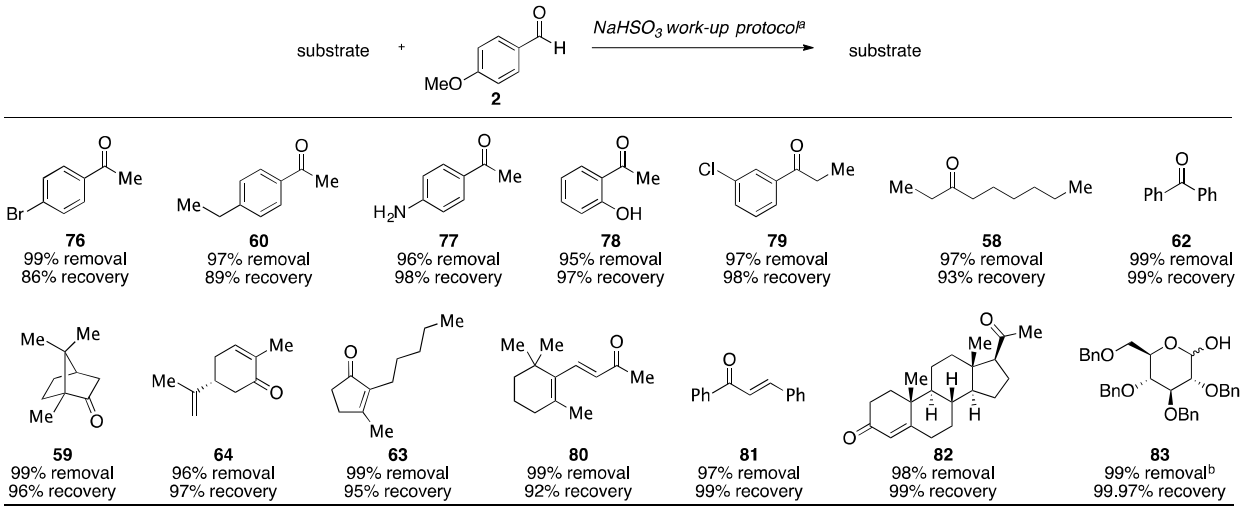


[a]Ketone (1.4 mmol) and benzyl butyrate (250 µL, 1.4 mmol) were dissolved in 5 mL MeOH, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. [b]DMF used in place of methanol. The aqueous layer was extracted twice. The organic layer was washed three times with water. [c]Required filtration to remove solid bisulfite adduct. [d]Pentane used in place of 10% EA/hexanes.

The high degree of differential reactivity between conjugated or slightly sterically-hindered ketones and reactive carbonyl compounds allows for selective separation. To demonstrate this selectivity, a variety of unreactive ketone substrates were mixed with anisaldehyde **2** and subjected to the bisulfite work-up conditions to measure the selectivity of the separation (Scheme 5). Aromatic methyl ketones **76** and **60** were recovered in 86% and 89% yield, respectively. 4-aminoacetophenone **77** and 2-hydroxyacetophenone **78** were more effectively recovered, likely due to the decreased electrophilicity of the carbonyls when conjugated to electron rich aromatic rings. Slightly sterically-hindered ethyl ketones **79** and **58** were both recovered in high yield from the separation conditions. Benzophenone **62** was recovered in 99% yield after the separation protocol. Sterically-hindered camphor **59** was also

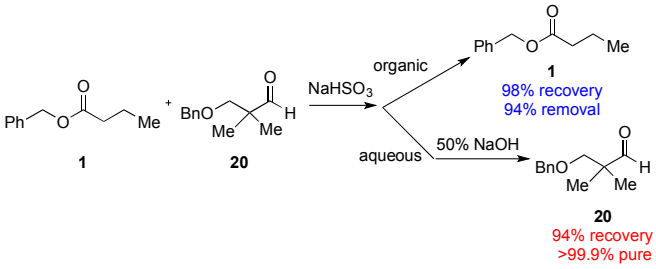
effectively separated. α,β-Unsaturated substrates carvone **64**, dihydrojasmone **63**, beta-ionone **80**, and chalcone **81** were all separated effectively from the more reactive aldehyde contaminant, with no observed conjugate addition products. Progesterone **82**, containing an α,β-unsaturated ketone and a sterically-hindered methyl ketone was recovered in 99% yield from the mixture after the bisulfite protocol. In addition to ketones, hemi-acetal **83** was also subjected to the work-up protocol to demonstrate the selectivity of the work-up. Though the hemi-acetal pyranose **83** is in equilibrium with its open-chain aldehyde form, the rate of this isomerization is slow relative to the timeframe of the work-up,[36] allowing for selective removal of anisaldehyde. These results demonstrate the discrimination possible among carbonyl compounds of differing reactivities.

Scheme 5. Separation of ketones and a cyclic hemi-acetal from anisaldehyde using the sodium bisulfite work-up protocol.



[a]Ketone (1.4 mmol) and anisaldehyde (175 µL, 1.4 mmol) were dissolved in 5 mL MeOH, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. [b]Pyranose **83** (0.28 mmol) and anisaldehyde (35 µL, 0.29 mmol) were dissolved in 5 mL DMF, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL EA. The organic layer was washed three times with 25 mL H_2O.

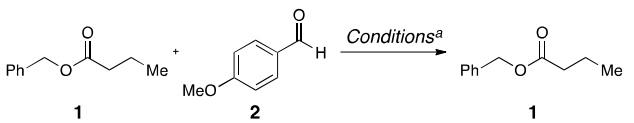
Scheme 6. Aldehyde recovery by basification of aqueous layer.



In some cases, recovery of the aldehyde is desirable, particularly when the aldehyde is not commercially available. Bisulfite adduct formation is reversible, and is known to occur under both acidic and basic conditions. We found that basification of the aqueous layer with 50%

sodium hydroxide followed by extraction allowed for facile recovery of aldehyde **20** from a mixture with benzyl butyrate in 94% recovery and in greater than 99.9% purity (Scheme 6). Acidification with concentrated hydrochloric acid was not nearly as effective as basification; aldehyde **20** was only recovered in 33% yield under these conditions. Basification of the aqueous layer provides a convenient method for aldehyde re-isolation.

The scale of the work-up protocol was selected for ease of use, precision of measurements, and minimization of reagents. For large scale work-ups, however, it is increasingly important to use minimal amounts of solvents to improve safety, cost, and convenience. To test the limits of the protocol, we re-examined the separation of benzyl butyrate from anisaldehyde (Table 4). Doubling the amount of substrate and contaminant aldehyde dramatically decreased the decontamination factor from 110 to 5.8 (entry 2). Increasing the scale of the substrates by a factor of five lowered the decontamination factor further to 2.6 (entry 3). Interestingly, when the scale was increased tenfold, a precipitate was observed between the two layers. Water was added until the precipitate dissolved to aid in separation. This improved the decontamination factor to 3.7, presumably due to better solvation and removal of the bisulfite adduct (entry 3 vs. entry 4). Increasing the amount of miscible solvent improved the separation dramatically, presumably due to increased contact between the aldehyde and aqueous layer created by the miscible solvent (entry 2 vs entry 5). When these conditions were applied to a fivefold increase in substrate, precipitate was observed and additional water was added until complete solvation was achieved, resulting in an improved decontamination factor of 50 (entry 6). These conditions were repeated for a tenfold increase in substrate, requiring an additional 50 mL of water to dissolve the precipitate. Even at this high concentration, anisaldehyde was removed in 97% from the mixture. Decreasing the amount of saturated sodium bisulfite resulted in complete solidification of the mixture, presumably due to insufficient water available to solvate the bisulfite adduct. Although water was successfully added to dissolve the solid, solidification in a separatory funnel is inconvenient and tedious to unclog, and thus should be avoided. Interestingly, the removal rate was improved under these conditions, presumably due to the slight exotherm observed upon solidification of the mixture. Clearly, the amount of bisulfite in the saturated solution is sufficient even at these high aldehyde concentrations. The main concern is solvation of the resultant bisulfite adduct and avoiding the formation of a solid aqueous layer. We next re-examined the small-scale conditions by lowering the amount of bisulfite, since the results at large scale showed that much less was required. Interestingly, when the amount of bisulfite was lowered, even better results were obtained, as compared to the standard conditions (entries 9-11). Anisaldehyde was not detected even when only 1 mL of saturated sodium bisulfite was employed. This surprising observation is likely due to improved solubility of the adduct in the aqueous layer at higher methanol concentrations and lower salt concentrations.



1 **2** **1**

Entry	mmol **1**	mmol **2**	MeOH	$NaHSO_{3\ (aq)}$	H_2O	DF[b]	Removal[c]
1	1.4	1.4	5 mL	25 mL	25 mL	110	99.1%
2	2.8	2.8	5 mL	25 mL	25 mL	5.8	83%
3	7.0	7.0	5 mL	25 mL	25 mL	2.6	61%
4	14.0	14.0	5 mL	25 mL	75 mL[d]	3.7	73%
5	2.8	2.8	10 mL	25 mL	25 mL	22	95%
6	7.0	7.0	10 mL	25 mL	75 mL[d]	50	98%
7	14.0	14.0	10 mL	25 mL	125 mL[d]	32	97%
8[e]	14.0	14.0	10 mL	15 mL	125 mL	100	99%
9	1.4	1.4	5 mL	10 mL	25 mL	>1000	>99.9%
10	1.4	1.4	5 mL	4 mL	25 mL	>1000	>99.9%
11	1.4	1.4	5 mL	1 mL	25 mL	>1000	>99.9%

Table 4. Separation of anisaldehyde from benzyl butyrate using sodium bisulfite. Anisaldehyde and benzyl butyrate were dissolved in methanol, saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with H_2O, and extracted with 25 mL 10% EA/hexanes. [b]Decontamination factor. [c]Determined by ^1H NMR analysis. [d]Water added until precipitate dissolved. [e]Solidified upon shaking.

Conclusion

In conclusion, the developed bisulfite protocol is an effective way to separate aromatic and aliphatic aldehydes from substrates containing a wide variety of functional groups. In addition, unhindered methyl ketones and unconjugated cyclic or highly electrophilic ketones can also be removed from mixtures, while unreactive aromatic, conjugated, or slightly sterically-hindered ketones are retained. Unwanted reactivity of electron-rich alkene-containing substrates can be mitigated by employing hexanes as the immiscible solvent, by taking advantage of the low sulfur dioxide solubility of nonpolar solvents. Highly nonpolar substrates can also be successfully removed by using dimethylformamide as the miscible solvent to improve mixing of the substrate with the bisulfite ion. The workup can be scaled up successfully to minimize the amount of solvents employed for separation. The mildness of these conditions and the ease of the protocol, together with the ubiquity of aldehydes in organic synthesis, should make this work-up protocol widely applicable to the daily task of separation encountered by many organic chemists.

Experimental

Reactants and reagents were purchased from commercial sources and used without further purification, except for o-anisidine **42**, α-terpineol **45,** α-pinene **46**, and alloocimene **57**, which were distilled prior to use. All reactions were carried out under a N_2 atmosphere, except for the extraction procedures, which were done under ambient atmospheric conditions.

Aldehyde synthesis. The synthesis of 3-oxopropyl isobutyrate **16** is representative. 1,3-Propanediol (1.8 mL, 25 mmol) was dissolved in THF (60 mL, 0.4M) and cooled to -78 °C. *n*-BuLi (1.6M hexanes, 16 mL, 25.6 mmol) was added slowly and the reaction was stirred for 5 minutes and then isobutyrylchloride (2.7 mL, 26 mmol) was added and the reaction was stirred for 14 hours while slowly warming to ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed gradiently with 15-50% EA/hexanes to give the known mono-acylated alcohol 3-hydroxypropyl isobutyrate[37] (957.7 mg, 26% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.24 (t, *J* = 6.1 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 2.56 (septet, *J* = 7.0 Hz, 1H), 1.80-1.92 (m, 3H), 1.17 (d, *J* = 7.0 Hz, 6H) ppm.
3-hydroxypropyl isobutyrate (957.7 mg, 6.55 mmol) was dissolved in DCM (2.6 mL, 2.5M) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) (11.7 mg, 0.075 mmol) was added. Potassium bromide (93.0 mg, 0.78 mmol) dissolved in water (1.0 mL) was then added and the reaction was cooled to 0 °C. Sodium hypochlorite (15% available chlorine, 5.4 mL) with sodium bicarbonate (221.1 mg, 2.6 mmol) suspended in the solution was added dropwise to give an orange-brown color. After 15 minutes the reaction was warmed to ambient temperature and stirred for 15 minutes. The reaction was diluted with DCM, washed with water, and the aqueous layer was extracted three times with DCM, dried ($MgSO_4$) filtered, and concentrated *in vacuo* to give the known title compound **16**[12,13] (397.0 mg, 42% yield) as a clear oil that was pure by ^{1}H NMR.

3-oxopropyl isobutyrate 16. ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.79 (t, *J* = 1.6 Hz, 1H), 4.41 (t, *J* = 6.1 Hz, 2H), 2.76 (dt, *J* = 1.6, 6.1 Hz, 2H), 2.53 (septet, *J* = 7.0 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 6H) ppm.

3-Acetoxy-2-methylpropanal 19. The procedure was the same as for 3-oxopropyl isobutyrate **16**, except 2-methyl-1,3-propanediol (0.44 mL, 5 mmol) and acetic anhydride (0.48 mL, 5.1 mmol) were used in the mono-acylation step. The known 3-acetoxy-2-methylpropanal **19**[14] (257.8 mg, 39% yield over 2 steps) was obtained as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.70 (d, *J* = 1.4 Hz, 1H), 4.30 (m, 2H), 2.69 (m, 1H), 2.05 (s, 3H), 1.16 (d, *J* = 7.2 Hz, 3H) ppm.

3-Acetoxy-2,2-dimethylpropanal 21. The procedure was the same as for 3-oxopropyl isobutyrate **16**, except 2,2-dimethyl-1,3-propanediol (2.0039 g, 20 mmol) and acetic anhydride (2.1 mL, 22 mmol) were used in the mono-acylation step. The known 3-acetoxy-2,2-dimethylpropanal **21**[17] (705.4 mg, 25% yield over 2 steps) was obtained as a clear oil after chromatography with 2-12% EA/hexane. ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.53 (s, 1H), 4.11 (s, 2H), 2.04 (s, 3H), 1.11 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$), δ 203.5, 170.8, 67.9, 46.2, 20.7, 18.8 ppm.

Substrate synthesis.
4-Pentyn-1-yl benzoate 52. 4-pentyn-1-ol (0.46 mL, 5 mmol) was dissolved in THF (20 mL, 0.4M) and cooled to -78 °C. *n*-BuLi (1.6M hexanes, 3.2 mL, 5.1 mmol) was added slowly and the reaction was stirred for 5 minutes and then benzoyl chloride (0.58 mL, 5.0 mmol) was added and the reaction was stirred for 14 hours while slowly warming to ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed gradiently with

0-5% EA/hexanes to give the known title compound[24] (883.0 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.05 (dd, *J* = 1.4, 8.5 Hz, 2H), 7.56 (tt, *J* = 1.4, 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 4.34 (t, *J* = 6.2 Hz, 2H), 2.39 (dt, *J* = 2.7, 7.1 Hz, 2H), 1.96-2.05 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$), δ 166.5, 132.9, 130.2, 129.5, 128.3, 83.0, 69.1, 63.4, 27.7, 15.3 ppm.

3-Pentyn-1-ol, benzoate 53. 3-pentyn-1-ol (0.46 mL, 5 mmol) was dissolved in THF (20 mL, 0.4M) and cooled to -78 °C. *n*-BuLi (1.6M hexanes, 3.2 mL, 5.1 mmol) was added slowly and the reaction was stirred for 5 minutes and then benzoyl chloride (0.58 mL, 5.0 mmol) was added and the reaction was stirred for 14 hours while slowly warming to ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed gradiently with 0-3% EA/hexanes to give the known title compound[25] (740.6 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.07 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.56 (tt, *J* = 1.3, 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 4.38 (t, *J* = 7.0 Hz, 2H), 2.60 (m, 2H), 1.79 (t, *J* = 2.6 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$), δ 166.1, 132.8, 130.0, 129.5, 1282, 77.2, 74.5, 63.1, 19.2, 3.3 ppm.

2-Benzylcycloheptanone 67. Diisopropylamine (0.46 mL, 3.3 mmol) was dissolved in THF (5 mL) and cooled to -78 °C. *n*-BuLi (1.6M hexanes, 2.1 mL, 3.4 mmol) was added slowly and the reaction was stirred for 15 minutes and then cycloheptanone (0.35 mL, 3.0 mmol) was added. After 15 minutes, benzyl bromide (0.71 mL, 6.0 mmol) was added and the reaction was stirred for 14 hours while slowly warming to ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed gradiently with 0-4% EA/hexanes to give the known title compound[33] (470.6 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.27 (t, *J* = 7.0 Hz, 2H), 7.14-7.25 (m, 3H), 3.08 (dd, *J* = 5.8, 13.7 Hz, 1H), 2.82 (m, 1H), 2.56 (dd, *J* = 8.5, 13.8 Hz, 2H), 2.43-2.50 (m, 2H), 1.77-1.86 (m, 4H), 1.56-1.65 (m, 1H), 1.25-1.36 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$), δ 215.6, 139.9, 129.1, 128.3, 126.0, 53.6, 43.1, 37.8, 30.3, 29.2, 28.6, 24.2 ppm.

Standard work-up procedure for aldehyde and ketone removal.
Substrate (1.4 mmol) and aldehyde (1.4 mmol) were dissolved in 5 mL MeOH, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the recovered substrate.

Work-up procedure for non-polar aldehyde and ketone removal.
Substrate (1.4 mmol) and aldehyde (1.4 mmol) were dissolved in 10 mL DMF, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. The aqueous layer was extracted with 25 mL of 10% EA/hexanes. The combined organic layers were washed three times with H_2O (25 mL, 10 mL, 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the recovered substrate.

Work-up procedure for isolation of both aldehyde and ketone.

Benzyl butyrate (250 µL, 1.4 mmol) and aldehyde **20** (275.0 mg, 1.4 mmol) were dissolved in 10 mL DMF, 25 mL saturated $NaHSO_{3(aq)}$ added, shaken for approximately 30 s, diluted with 25 mL H_2O, and extracted with 25 mL 10% EA/hexanes. The aqueous layer was extracted with 25 mL of 10% EA/hexanes three times. The organic layers were washed three times with H_2O (25 mL, 10 mL, 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield recovered benzyl butyrate (261.3 mg, 98% recovery). The combined aqueous layers were basified with 50% sodium hydroxide and extracted with 25 mL of 10% EA/hexanes three times. The organic layers were washed three times with H_2O (25 mL, 10 mL, 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield recovered aldehyde **20** (261.3 mg, 95% recovery).

Acknowledgements

Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research. We are grateful to the National Science Foundation (CHE-0619275 and CHE-0963165) for renovation and instrumentation grants that supported this research.

Supporting Information. ^{1}H NMR for aldehydes **16**, **19** and **21**, substrates **52**, **53**, and **67** and for all separations is available.

References

(1) Wilson, I. D.; Adlard, E. R.; Cooke, M.; Poole, C. F. *Encyclopedia of Separation Science*; Encyclopedia of Separation Science; Academic Press, 2000.
(2) Caron, S. In *Practical Synthetic Organic Chemistry: Reactions, Principles, and Techniques*; Wiley, 2011; pp 75–76.
(3) Clayden, J.; Greeves, N.; Warren, S. In *Organic Chemistry*; Oxford University Press: New York, 2001; pp 138–140.
(4) Betti, M.; Genesio, E.; Marconi, G.; Sanna Coccone, S.; Wiedenau, P. *Org. Process Res. Dev.* **2014**, *18* (6), 699–708.
(5) Kjell, D. P.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64* (15), 5722–5724.
(6) Cox, J. P.; Cox, R. W. D. Aldehyde and/or antimicrobial composition for reduction of animal waste odors. US5807587 A, September 15, 1998.
(7) Malle, G. Bisulfite combinations of aldehydes and their use for the permanent deformation of hair. EP0257256 A2, April 23, 2004.
(8) Guthrie, J. P.; Wu, Y.-Y.; Bannister, A. R.; Peiris, S.; Povar, I.; Wilson, E. A.; Wang, Q. *Can. J. Chem.* **2015**, *93* (2), 227–233.
(9) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101* (12), 3288–3294.
(10) Olson, T. M.; Boyce, S. D.; Hoffmann, M. R. *J. Phys. Chem.* **1986**, *90* (11), 2482–2488.
(11) Olson, T. M.; Hoffmann, M. R. *J. Phys. Chem.* **1988**, *92* (14), 4246–4253.
(12) Araki, T.; Hayase, S.; Nakamura, A. *J. Polym. Sci. Polym. Chem. Ed.* **1983**, *21* (6), 1671–1679.
(13) Zhang, M.; Ke, L.; Zhao, Q.; Wu, J. Method for simultaneous production of 1,3-propanediol and 1,2-propanediol. CN 102372603, March 14, 2012.
(14) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem. Int. Ed.* **2010**, *49* (24), 4047–4050.

(15) Yang, Y.; Wang, J.; Kayser, M. *Tetrahedron Asymmetry* **2007**, *18* (17), 2021–2029.
(16) Kuranaga, T.; Sesoko, Y.; Sakata, K.; Maeda, N.; Hayata, A.; Inoue, M. *J. Am. Chem. Soc.* **2013**, *135* (14), 5467–5474.
(17) Brown, R. F.; Van Gulick, N. M. *J. Am. Chem. Soc.* **1955**, *77* (5), 1089–1092.
(18) Masilamani, D.; Manahan, E. H.; Vitrone, J.; Rogic, M. M. *J. Org. Chem.* **1983**, *48* (25), 4918–4931.
(19) Masilamani, D.; Rogic, M. M. *J. Am. Chem. Soc.* **1978**, *100* (14), 4634–4635.
(20) Makitra, R. G.; Kal'muk, S. D.; Bryk, D. V.; Polyuzhin, I. P. *Russ. J. Inorg. Chem.* **2010**, *55* (8), 1322–1329.
(21) van Dam, M. H. H.; Lamine, A. S.; Roizard, D.; Lochon, P.; Roizard, C. *Ind. Eng. Chem. Res.* **1997**, *36* (11), 4628–4637.
(22) Li, H.; Jiao, X.; Chen, W. *Phys. Chem. Liq.* **2014**, *52* (2), 349–353.
(23) Su, W.; Chen, J.; Wu, H.; Jin, C. *J. Org. Chem.* **2007**, *72* (12), 4524–4527.
(24) Stevens, B. D.; Nelson, S. G. *J. Org. Chem.* **2005**, *70* (11), 4375–4379.
(25) Haberlag, B.; Wu, X.; Brandhorst, K.; Grunenberg, J.; Daniliuc, C. G.; Jones, P. G.; Tamm, M. *Chem. - Eur. J.* **2010**, *16* (29), 8868–8877.
(26) Cunliffe, A. V.; Grinter, R.; Harris, R. K. *J. Magn. Reson. 1969* **1970**, *2* (2), 200–208.
(27) Fenselau, C.; Young, J. L.; Landis, W. R. *Org. Mass Spectrom.* **1970**, *3* (8), 1085–1088.
(28) Shibamoto, T.; Enomoto, Y.; Akiyama, T. *Food Chem.* **1981**, *7* (3), 219–225.
(29) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352* (1), 103–107.
(30) Cerichelli, G.; Cerritelli, S.; Chiarini, M.; De Maria, P.; Fontana, A. *Chem. - Eur. J.* **2002**, *8* (22), 5204–5210.
(31) Wang, S.; Chen, G.; Kayser, M. M.; Iwaki, H.; Lau, P. C. K.; Hasegawa, Y. *Can. J. Chem.* **2002**, *80* (6), 613–621.
(32) Taaning, R. H.; Thim, L.; Karaffa, J.; Campana, A. G.; Hansen, A.-M.; Skrydstrup, T. *Tetrahedron* **2008**, *64* (52), 11884–11895.
(33) Chhatwal, V. K.; Gautam, R. K.; Saharia, G. S. *J. Inst. Chem. India* **1983**, *55* (2), 55–57.
(34) Jana, R.; Tunge, J. A. *J. Org. Chem.* **2011**, *76* (20), 8376–8385.
(35) Lin, S.; Lu, X. *Tetrahedron Lett.* **2006**, *47* (40), 7167–7170.
(36) Jawad, R.; Drake, A. F.; Elleman, C.; Martin, G. P.; Warren, F. J.; Perston, B. B.; Ellis, P. R.; Hassoun, M. A.; Royall, P. G. *Mol. Pharm.* **2014**, *11* (7), 2224–2238.
(37) Yoshida, K.; Furuta, T.; Kawabata, T. *Angew. Chem. Int. Ed.* **2011**, *50* (21), 4888–4892.