Video Article

Separation of Aldehydes and Reactive Ketones from Mixtures Using a Bisulfite Extraction Protocol

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Abstract

The purification of organic compounds is an essential component of routine synthetic operations. The ability to remove contaminants into an aqueous layer by generating a charged structure provides an opportunity to use extraction as a simple purification technique. By combining the use of a miscible organic solvent with saturated sodium bisulfite, aldehydes and reactive ketones can be successfully transformed into charged bisulfite adducts that can then be separated from other organic components of a mixture by the introduction of an immiscible organic layer. Here, we describe a simple protocol for the removal of aldehydes, including sterically-hindered neopentyl aldehydes and some ketones, from chemical mixtures. Ketones can be separated if they are sterically unhindered cyclic or methyl ketones. For aliphatic aldehydes and ketones, dimethylformamide is used as the miscible solvent to improve removal rates. The bisulfite addition reaction can be reversed by basification of the aqueous layer, allowing for the re-isolation of the reactive carbonyl component of a mixture.

Video Link

The video component of this article can be found at https://www.jove.com/video/57639/

Introduction

The separation of components of mixtures from one another is essential to the preparation of pure materials. The method described herein allows for the facile separation of aldehydes and sterically unhindered cyclic and methyl ketones from other organic molecules[1]. The technique relies on the reactivity of bisulfite with the carbonyl group to create a charged adduct that can be separated into an aqueous layer, while other components separate into an immiscible organic layer. The key to achieving reactivity between bisulfite and the carbonyl is the use of a miscible solvent, which allows the reaction to take place prior to the separation into separate phases. Without the addition of the miscible solvent minimal separation is obtained, presumably due to poor contact between the hydrophilic bisulfite and the hydrophobic organics.

The advantage of this separation method for purification is the ease of the protocol. Liquid-liquid extraction is a simple operation to perform, and can be carried out on large scale. Alternative purification techniques, such as column chromatography, are much more expensive, time-consuming, and challenging to perform on large scale and require sufficient differentiation of the components in terms of polarity. Purifying by recrystallization or distillation requires sufficient differentiation between the solubility or boiling points of the components of the mixture, respectively. Because bisulfite extraction relies on the difference in reactivity of the carbonyl group of aldehydes and ketones, compounds with similar solubility, boiling points, or polarities can be effectively separated. Other chemical separation methods exist for the selective separation of aldehydes and ketones from mixtures, for example, the selective formation of oximes[2], cyclic acetals[3], or mercaptal[4] formation. These methods require an additional step to separate the formed species from the mixture, because the product is not water soluble and therefore cannot be separated by a simple extraction protocol. Aldehyde oxidation to form removable carboxylic acids is another reported technique[5], but the required oxidation step is less chemoselective than the mild bisulfite conditions described herein, and requires the use of oxygen gas and a cobalt catalyst.

This method is applicable to the separation of aldehydes (**Figure 1**) and sterically-unhindered cyclic and methyl ketones (**Figure 2**) from molecules that do not contain these functional groups. Particularly reactive ketones, such as α-keto esters are also removed using this process. Alkanes, alkenes, dienes, alkynes, esters, amides, carboxylic acids, alkyl halides, alcohols, phenols, nitriles, benzyl chlorides, epoxides, anilines, acetals, and slightly hindered, α,β-unsaturated, or aryl ketones are all unreactive under the conditions and can be separated from the aldehyde or reactive ketone component of the mixture (**Figures 2** and **Figure 3**). Ethyl ketones or α-substituted cyclic ketones, for example, are sufficiently hindered and are therefore separable from aldehydes and more reactive ketones. When using alkenes, hexane is recommended as the immiscible solvent to prevent unwanted decomposition due to sulfur dioxide present in the bisulfite solution. The functional group compatibility of the bisulfite extraction protocol is extremely broad, and is therefore applicable to an extremely wide range of separations, if the carbonyl contaminant to be separated from the mixture is either an aldehyde or an unhindered methyl or cyclic ketone. Less reactive ketones do not react with bisulfite under these conditions and are therefore not removed.

Protocol

1. Standard Protocol for The Separation of Aromatic Aldehydes from a Mixture. Example: Separation of Benzyl Butyrate from a 1:1 Mixture with Anisaldehyde.

1. Dissolve 175 µL of anisaldehyde and 250 µL of benzyl butyrate in 5 mL of methanol and transfer the solution to a separatory funnel.
   Caution: Sodium bisulfite can generate sulfur dioxide gas, thus this protocol should be carried out with proper ventilation, such as in a fume hood.
2. Add 1 mL of saturated aqueous sodium bisulfite and shake vigorously for approximately 30 s.
3. Add 25 mL of deionized water and 25 mL of 10% ethyl acetate/hexanes and shake vigorously.
4. Separate the layers. Dry the organic layer with anhydrous magnesium sulfate. Filter the solution to remove magnesium sulfate and concentrate *in vacuo* using a rotary evaporator.

2. Separation of Aliphatic Aldehydes and Ketones from a Mixture. Example: Separation of Benzyl Butyrate from a 1:1 Mixture with Benzylacetone.

1. Dissolve 213 µL of benzylacetone and 250 µL of benzyl butyrate in 10 mL of dimethylformamide and transfer the solution to a separatory funnel.
   Caution: Sodium bisulfite can generate sulfur dioxide gas, thus this protocol should be carried out with proper ventilation, such as in a fume hood.
2. Add 25 mL of saturated aqueous sodium bisulfite and shake vigorously for approximately 30 s.
3. Add 25 mL of deionized water and 25 mL of 10% ethyl acetate/hexanes and shake vigorously.
4. Separate the layers. Return the aqueous layer to the separatory funnel, add 25 mL of 10% ethyl acetate/hexanes and shake vigorously. Drain the aqueous layer, leaving the organic layer in the separatory funnel. Add the previous organic layer back to the separatory funnel.
5. Wash the combined organic layers three times with deionized water (10 mL for each wash). Dry the organic layer with anhydrous magnesium sulfate. Filter the solution to remove magnesium sulfate and concentrate *in vacuo* using a rotary evaporator.

3. Separation of Aldehydes from a Mixture Containing an Alkene. Example: Separation of Benzyl Butyrate from a 1:1 Mixture with Citronellal.

1. Dissolve 255 µL of citronellal and 250 µL of benzyl butyrate in 10 mL of dimethylformamide and transfer the solution to a separatory funnel.
   Caution: Sodium bisulfite can generate sulfur dioxide gas, thus this protocol should be carried out with proper ventilation, such as in a fume hood.
2. Add 25 mL of saturated aqueous sodium bisulfite and shake vigorously for approximately 30 s.
3. Add 25 mL of deionized water and 25 mL of hexanes and shake vigorously.
4. Separate the layers. Return the aqueous layer to the separatory funnel, add 25 mL hexanes and shake vigorously. Drain the aqueous layer, leaving the organic layer in the separatory funnel. Add the previous organic layer back to the separatory funnel.
5. Wash the combined organic layers three times with deionized water (10 mL for each wash). Dry the organic layer with anhydrous magnesium sulfate. Filter the solution to remove magnesium sulfate and concentrate *in vacuo* using a rotary evaporator.

4. Re-isolation of Aldehydes from a Mixture. Example: Separation of Piperonal from a 1:1 Mixture with Benzyl Butyrate.

1. Dissolve 217 mg of piperonal and 250 µL of benzyl butyrate in 5 mL of methanol and transfer the solution to a separatory funnel.
   Caution: Sodium bisulfite can generate sulfur dioxide gas, thus, this protocol should be carried out with proper ventilation, such as in a fume hood.
2. Add 1 mL of saturated aqueous sodium bisulfite and shake vigorously for approximately 30 s.
3. Add 25 mL of deionized water and 25 mL of 10% ethyl acetate/hexanes and shake vigorously.
4. Separate the layers. Return the aqueous layer back to the separatory funnel.
   1. Optional: Wash aqueous layer once with 25 mL of 10% ethyl acetate/hexanes to remove the small amount of remaining benzyl butyrate.

5. Add 25 mL of ethyl acetate and then add 50% sodium hydroxide until a pH strip indicates that the pH is 12. Shake vigorously.
   Caution: Gas evolution has been observed during this step and can cause pressure build-up. Make sure to properly vent the separatory funnel. Scaling up this procedure will make gas evolution more pronounced. Use caution.
6. Separate the layers. Return the aqueous layer to the separatory funnel and add 25 mL of ethyl acetate. Shake vigorously.
7. Separate the layers. Combine the organic layer with the organic layer from the previous step. Dry the combined organic layer with anhydrous magnesium sulfate. Filter the solution to remove magnesium sulfate and concentrate *in vacuo* using a rotary evaporator.

Representative Results

Procedure **1** for aldehyde removal is used for aromatic aldehydes. Procedure **2**, in which dimethylformamide is used as the miscible solvent, should be used for aliphatic aldehydes and ketones. Procedure **2** should also be used for mixtures that are not fully soluble in methanol. The material obtained from each of the protocols is analyzed for purity using ^{1}H NMR integration analysis and for recovery rate by mass. Typical purities and recoveries are greater than 95% (**Figure 1**). A successful separation is determined by the lack of ^{1}H NMR signals arising from the aldehyde or ketone component (**Figure 4** and **Figure 5**). Particularly diagnostic of a successful separation is the absence of a peak between 9 and 10 ppm when removing an aldehyde. If the separation does not occur, it may be due to a lack of sufficient bisulfite reactivity with the carbonyl compound. Conjugated ketones or sterically-hindered ketones are not removable using this method (**Figure 2**).

When using alkene-containing compounds, the recovered material has been observed to contain significant impurities when standard procedure **1** or **2** is employed, as determined by the presence of unidentified peaks in the ^{1}H NMR (**Figure 6**). For these substrates, modified procedure **3**, employing hexanes, limits the degradation caused by dissolved sulfur dioxide **(Figure 7**). If hexanes are too non-polar to dissolve the molecules of interest, as indicated by the formation of solids, chloroform can be used, though an increase in degradation is observed with this solvent relative to hexanes (**Figure 1**).

If re-isolation of the reactive aldehyde or ketone is desired, procedure **4** can be used to reverse the reaction and reform the carbonyl compound. An optional wash can be used to remove the small amount of remaining non-carbonyl component (**Figure 8** and **Figure 9**).

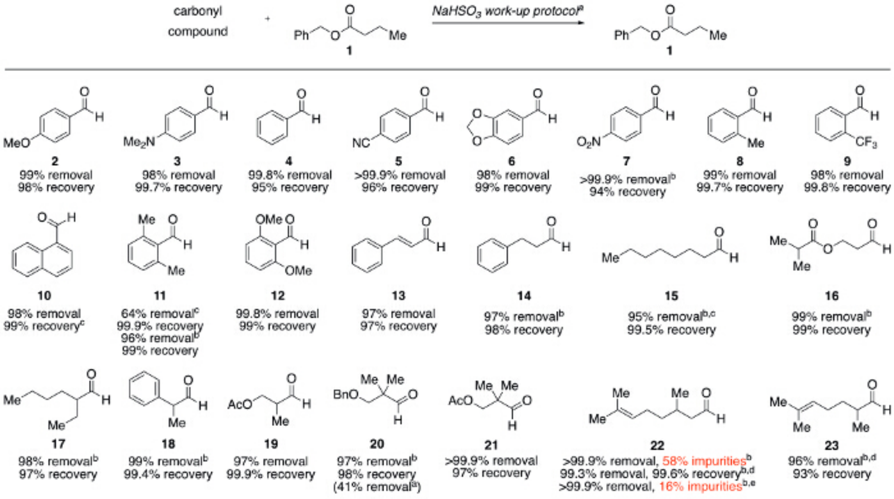

Figure 1. Representative separations indicate broad substrate scope with respect to the aldehyde partner[7]. (a) Benzyl butyrate (250 µL, 1.4 mmol) and aldehyde (1.4 mmol) were dissolved in 5 mL methanol, 25 mL of saturated aqueous sodium bisulfite added, shaken for approximately 30 s, diluted with 25 mL of water, and extracted with 25 mL of 10% ethyl acetate/hexanes. (b) Dimethylformamide used in place of methanol. (c) Required filtration through Celite. (d) Hexanes was used in place of 10% ethyl acetate/hexanes. (e) Chloroform was used in place of 10% ethyl acetate/hexanes. Note that some of these values are for unoptimized conditions. Using 1 mL of saturated aqueous sodium bisulfite gives higher removal rates for aromatic aldehydes. Please click here to view a larger version of this figure.

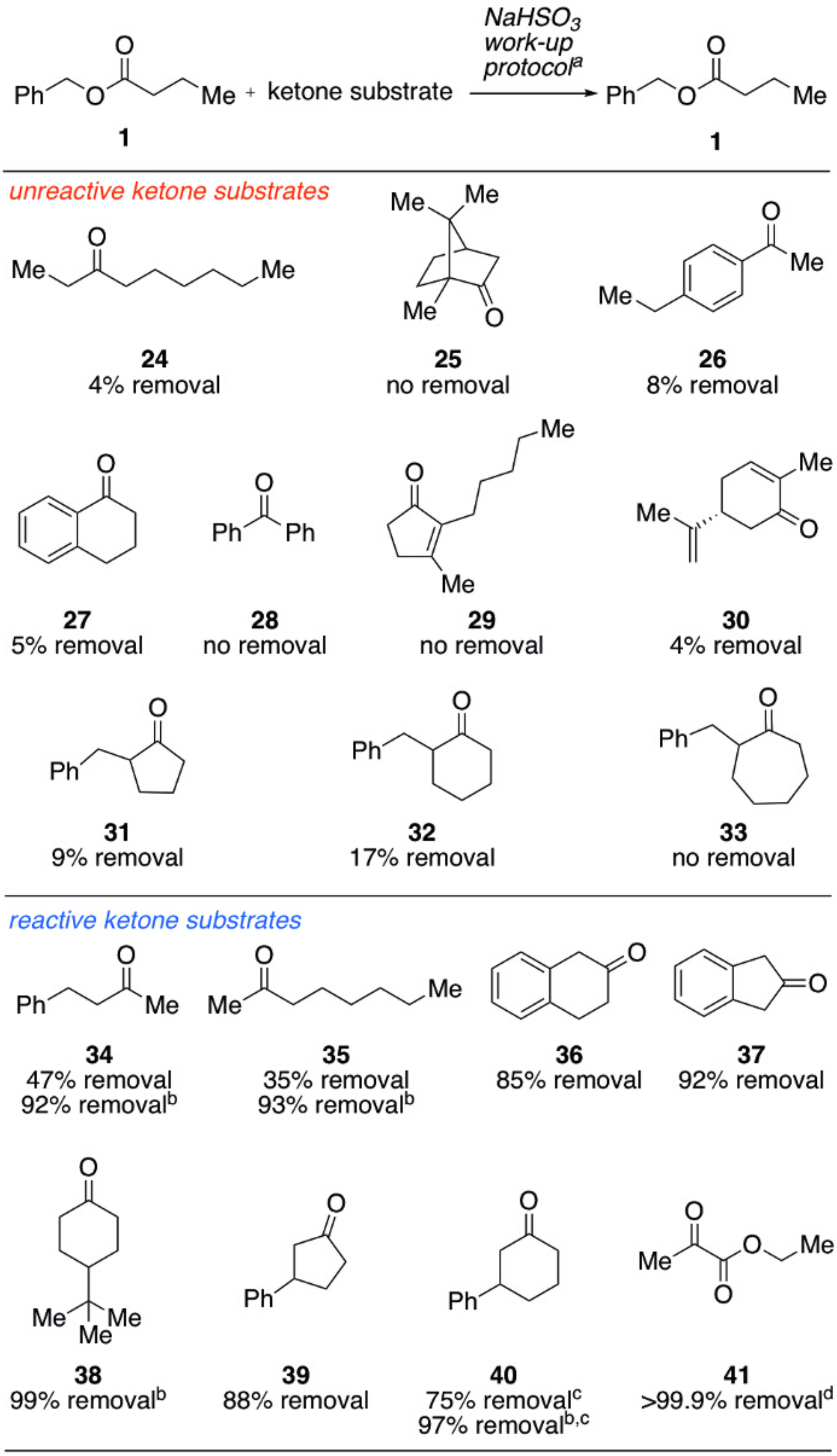

Figure 2. Ketones typically fall into two distinct categories: reactive and unreactive[7]. (a) Ketone (1.4 mmol) and benzyl butyrate (250 µL, 1.4 mmol) were dissolved in 5 mL of methanol, 25 mL of saturated aqueous sodium bisulfite added, shaken for approximately 30 s, diluted with 25 mL of water, and extracted with 25 mL of 10% ethyl acetate/hexanes. (b) Dimethylformamide 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% ethyl acetate/hexanes. Please click here to view a larger version of this figure.

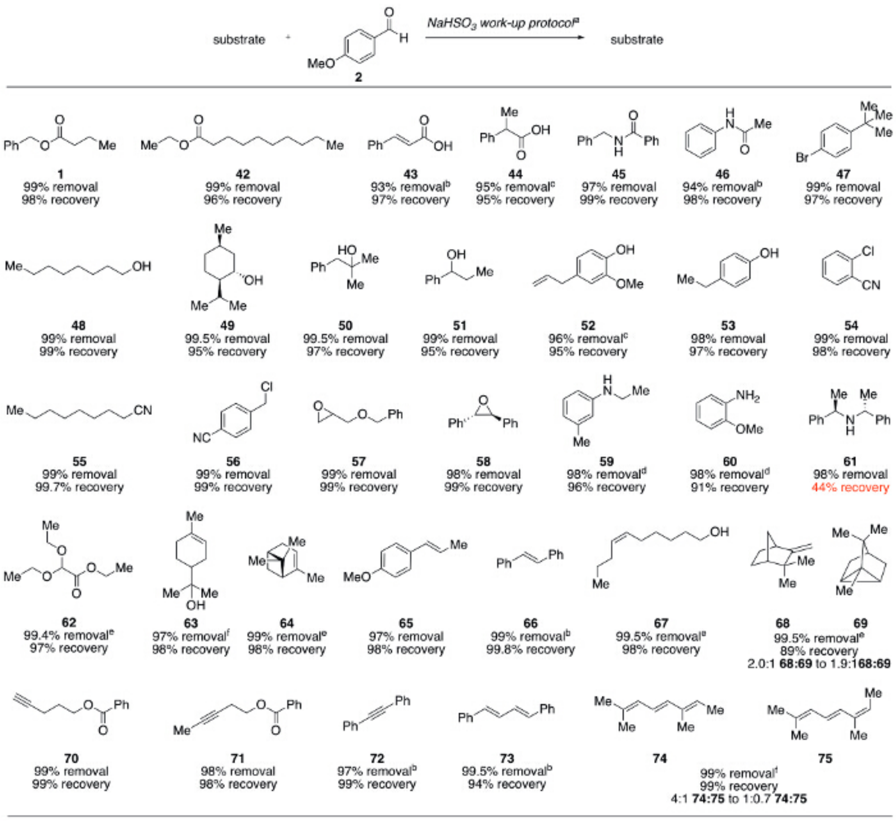

Figure 3. Representative separations indicate broad substrate scope with respect to the unreactive partner[7]. (a) Substrate (1.4 mmol) and anisaldehyde (175 µL, 1.4 mmol) were dissolved in 5 mL of methanol, 25 mL of saturated aqueous sodium bisulfite added, shaken for approximately 30 s, diluted with 25 mL of water, and extracted with 25 mL of 10% ethyl acetate/hexanes. (b) Dimethylformamide used in place of methanol. Ethyl acetate used in place of 10% ethyl acetate/hexanes. The aqueous layer was extracted twice. The organic layer was washed three times with water. (c) 50% Ethyl acetate/hexanes used in place of 10% ethyl acetate/hexanes. (d) The aqueous layer was extracted three times. (e) Pentane was used in place of 10% ethyl acetate/hexanes. (f) Hexanes was used in place of 10% ethyl acetate/hexanes. Note that these values are for unoptimized conditions. Using 1 mL of saturated aqueous sodium bisulfite gives higher removal rates for aromatic aldehydes. Please click here to view a larger version of this figure.

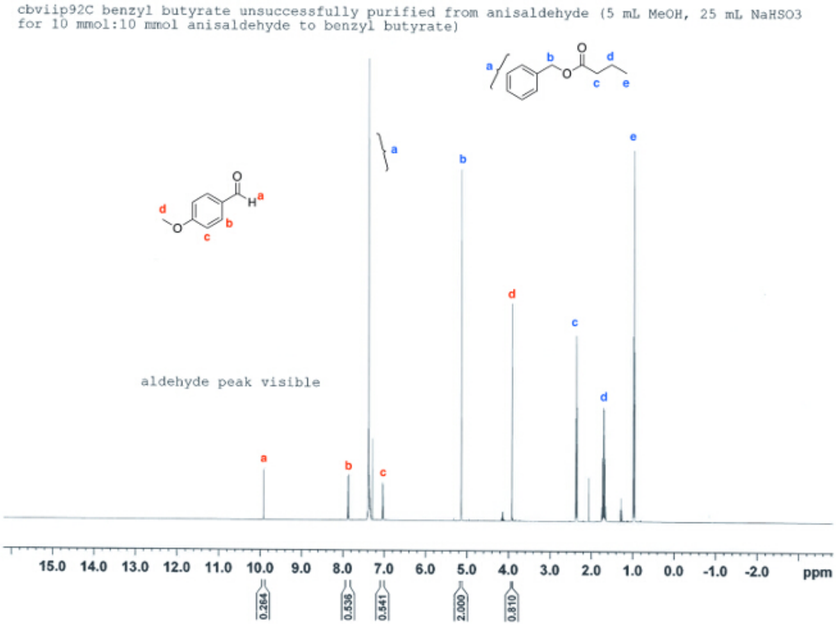

Figure 4. Representative ^{1}H NMR of an unsuccessful separation indicates the presence of the carbonyl component. All of the signals corresponding to the hydrogens of the carbonyl component are visible, but the presence of the aldehyde hydrogen signal, which typically comes between 9-10 ppm, is particularly diagnostic. Please click here to view a larger version of this figure.

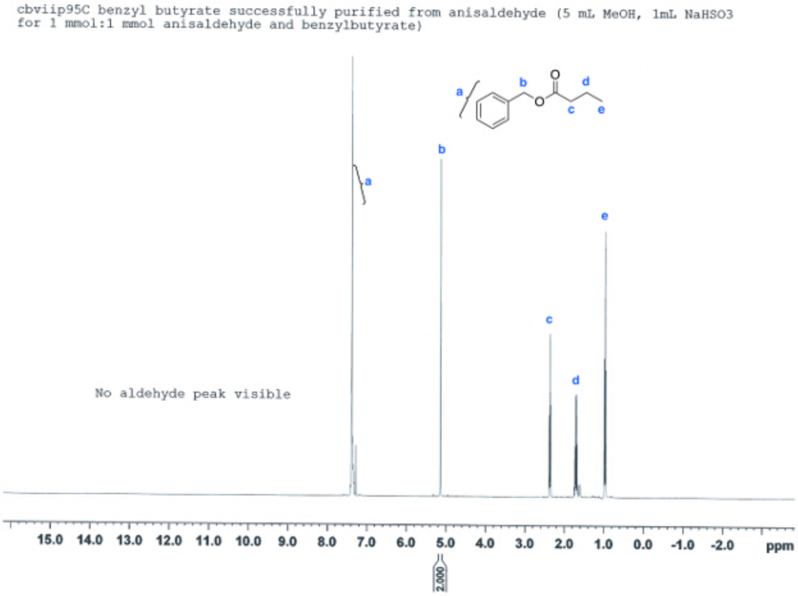

Figure 5. Representative ^{1}H NMR of a successful separation indicates complete removal of the reactive carbonyl component. None of the signals corresponding to the hydrogens of the carbonyl component are visible. The absence of the aldehyde hydrogen signal, which typically comes between 9-10 ppm, is particularly diagnostic in aldehyde removal. Please click here to view a larger version of this figure.

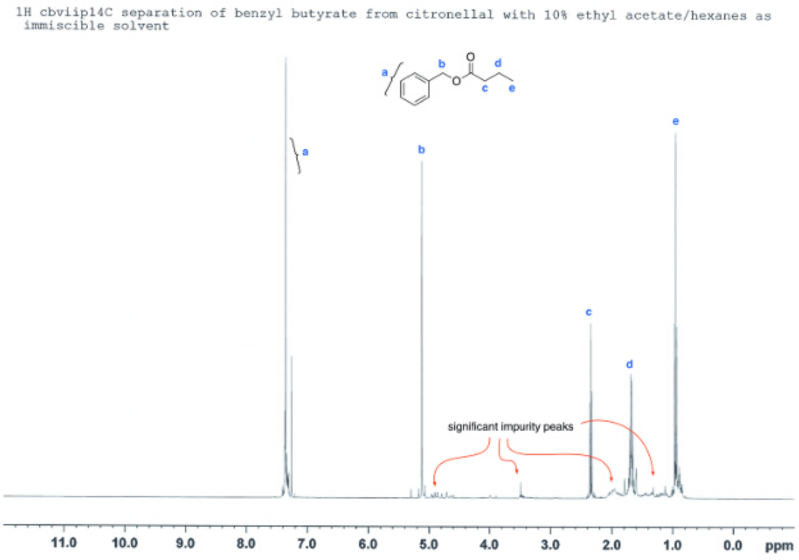

Figure 6. Representative ^{1}H NMR of an unsuccessful separation of an alkene-containing aldehyde shows a significant amount of impurity peaks. Please click here to view a larger version of this figure.

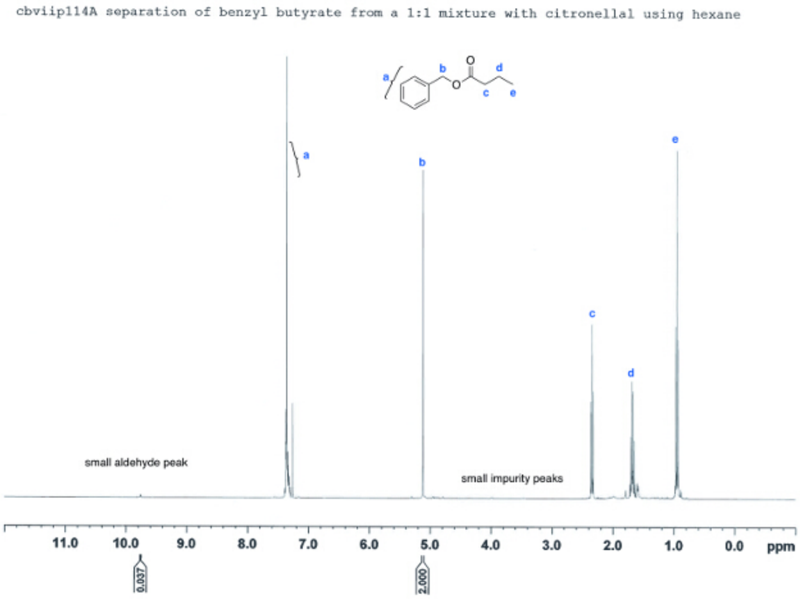

Figure 7. Representative ^{1}H NMR of a successful separation of an alkene-containing aldehyde shows only small impurity peaks and very little remaining aldehyde. Please click here to view a larger version of this figure.

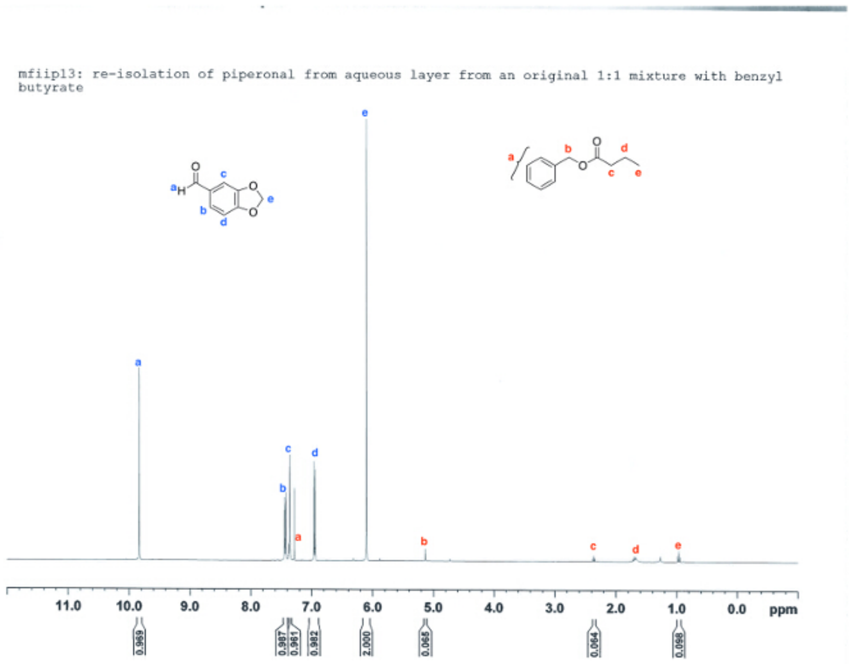

Figure 8. Representative ^{1}H NMR of a successful re-isolation of an aldehyde without optional wash. The presence of the non-carbonyl containing component is apparent, as the hydrogen signals corresponding to this compound are visible, but the amount of this contaminant is very small. Please click here to view a larger version of this figure.

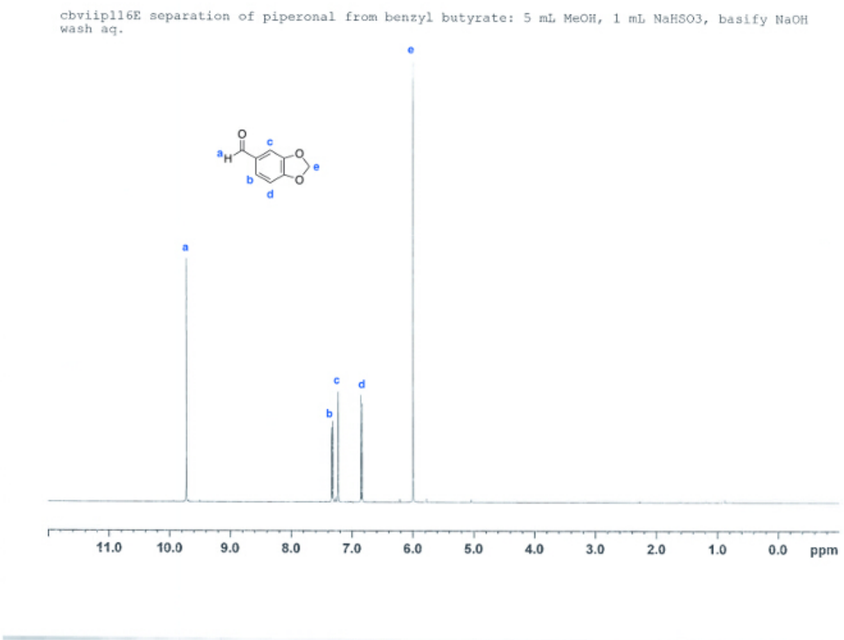

Figure 9. Representative ^{1}H NMR of a successful re-isolation of an aldehyde with the optional wash. The presence of the non-carbonyl component is nearly undetectable by ^{1}H NMR when the optional wash of the aqueous layer prior to basification is used. Please click here to view a larger version of this figure.

Discussion

Initial attempts to use the bisulfite reaction as a method to remove aldehydes using a typical two-phase extraction led to very low levels of removal. We hypothesized that the reaction was not fast enough to occur during the very limited time that the two layers were in contact. To increase the contact between the reactants, we developed a two-stage extraction protocol in which a water-miscible solvent is used initially to allow sufficient mixing of the reactants prior to the introduction of an immiscible solvent. The introduction of the immiscible solvent then allows for the separation of the charged bisulfite adduct from the uncharged organic component. The critical step in the protocol is the use of a miscible organic solvent that improves contact between the aqueous bisulfite and the organic soluble components. The identity of the miscible and immiscible solvents can be varied, as well as the ratio and identities of the reactive partners, the scale of the protocol, and the incorporation of a variety of additional extractions and/or washes to the protocol. This allows for the application and adaptation of this protocol to the separation of a wide range of chemical mixtures containing a reactive carbonyl component.

When adapting this protocol to novel chemical mixtures, care must be taken to avoid gas evolution, or excessive heat generation. The user should check chemical compatibility prior to attempting the bisulfite protocol. Bisulfite solutions can evolve sulfur dioxide gas, which can lead to the build-up of pressure. Bisulfite should be used with caution in combination with sodium carbonate, or sodium bicarbonate, due to the generation of carbon dioxide gas. It is recommended that bisulfite should be added slowly to control gas evolution, and the rapid generation of heat. The example separations described herein do not generate excessive heat or gas, but these safety concerns may arise when adapting the protocol to novel situations or when increasing the scale of the protocol. The protocol should be performed in a fume hood to ensure proper ventilation. Bisulfite is a reducing reagent and a weak acid, which should be taken into consideration for any new adaptation of this protocol. For example, most aliphatic amines are inappropriate substrates due to an unwanted acid-base reaction with bisulfite ion (**Figure 3**).

The identity of the miscible solvent can be varied with minimal impact on removal rates. In fact, most miscible solvents give enhanced removal rates relative to methanol, with the exception of tetrahydrofuran[1]. Methanol is preferable to most other miscible solvents because it partitions into the aqueous layer more effectively and any remaining solvent is easily removed during rotary evaporation due to its relatively high volatility. The second-best solvent, in terms of ease of use, is dimethylformamide. Dimethylformamide gives superior removal rates, but requires additional water washes to remove the residual solvent, due to its lower volatility and less favorable partition coefficient. Acetone should be avoided, due to competitive reaction with bisulfite. Dimethyl sulfoxide is also not recommended, due to the generation of unpleasant odors associated with the mildly reducing conditions. Because all miscible solvents tested were found to function comparably, it is possible to use this protocol directly on reaction mixtures employing these solvents, as long as all of the chemicals present are compatible. The volume of miscible solvent used has an impact on the removal rate[1], so the volume of the reaction, if used directly, should be adjusted appropriately, either by evaporation or dilution.

The identity of the immiscible solvent can also be varied (**Figure 1-3**). Non-polar solvents give the highest removal rates, while polar solvents give lower removal rates. It is recommended that the user select the least polar immiscible solvent that will dissolve the mixture. Bisulfite solutions are in equilibrium with sulfur dioxide gas, which can cause unwanted side reactions, particularly with alkenes[6,7]. The solubility of sulfur dioxide is lower in non-polar solvents[8,9,10]. When applying this method to alkene-containing compounds, the use of hexanes, pentane, or petroleum ether is recommended to limit the generation of impurities during the extraction protocol caused by sulfur dioxide. Since these solvents do not dissolve polar organic compounds, however, chloroform may be an appropriate alternative for mixtures containing polar components. It is not as effective as aliphatic solvents at minimizing unwanted decomposition, but gives improved results relative to the use of 10% ethyl acetate/hexanes.

Adaptation to novel chemical mixtures may require the optimization of the identity and amounts of both the immiscible and miscible solvents. Aromatic aldehydes are particularly good substrates for the bisulfite protocol, allowing for the use of the more convenient methanol protocol. Aliphatic aldehydes and ketones give lower removal rates compared to aromatic aldehydes, therefore to maintain high removal rates, dimethylformamide is used for these substrates. This protocol was optimized for the separation of equimolar ratios of reactive and non-reactive components. Adjustments to the protocol should be made based on the initial ratios of the components in the original sample for novel chemical mixtures. For example, if only trace aldehyde needs to be removed, procedure 1 may be the more appropriate choice. When selecting, use procedure 1 for a simpler and less time-consuming separation, and procedure 2 for higher purity for the recovered material.

When performing this protocol, there are several observations that can help the user adjust the protocol for their particular chemical scenario. If the mixture does not fully dissolve in the miscible solvent (step 1.1), a different miscible solvent should be selected that better matches the polarity of the particular chemical mixture under examination. When bisulfite is added (step 1.2), a cloudy white precipitate is often observed. This precipitate is the bisulfite adduct. It is not always observed, since it may be soluble in the miscible solvent/aqueous bisulfite mixture. When water and an immiscible solvent are introduced (step 1.3), no solids should be apparent. If solids are observed, it is an indication that one or both components are not soluble in either the aqueous or organic layer. If the non-reactive component is not soluble, this problem can be solved by adjusting the identity of the immiscible solvent. For example, carboxylic acids are very polar, and therefore 10% ethyl acetate/hexanes are insufficiently solvating. Simply changing the miscible solvent to 50% ethyl acetate/hexanes allowed for excellent purification of cinnamic acid **43** from anisaldehyde (**Figure 3**). If the reactive component is insoluble, the amount of water can be increased to better dissolve the bisulfite adducts, or multiple water washes can be used to remove the bisulfite adduct. If the addition of twice the volume of water is insufficient to dissolve the bisulfite adduct, the mixture can also be filtered through Celite to remove the solid bisulfite adduct from the mixture before proceeding to the next step. Once the material has been dried and the solvent has been removed, analysis of the ^{1}H NMR and the mass balance can assist in troubleshooting the protocol. If the separation is poor, the mass will indicate the presence of the aldehyde or ketone, and the signals corresponding to the aldehyde or ketone will be observed in the ^{1}H NMR spectrum. If improved separation is required, procedure 2 is recommended. If peaks unassociated with either component are observed, decomposition due to sulfur dioxide may have occurred. For these situations, procedure 3 is recommended.

The bisulfite protocol can also be used to re-isolate the reactive component by reversing the bisulfite addition reaction using procedure 4. This can be done by basification of the aqueous layer and extraction with an immiscible solvent. The identity of the base can be varied. Sodium hydroxide is recommended for complete reversal of the reaction. For enolizable carbonyl compounds, a weaker base should be used to prevent deprotonation. This prevents unwanted side reactions, such as the aldol reaction[11]. If the carbonyl component has an enolizable α-chiral center, epimerization or racemization is also of concern. The appropriate base will vary depending on the pKa of the substrate. Sodium carbonate is not recommended, due to the generation of carbon dioxide gas upon addition to the bisulfite adduct-containing aqueous layer, which can create a hazardous situation unless carefully controlled. We recommend sodium phosphate tribasic. The reversion reaction is pH dependent, therefore the reaction will not be as favored when using weaker bases. To improve recovery, La Châtelier's principle can be exploited by employing a large excess of the base to help push the reaction forward. Multiple extractions are also recommended to increase recovery of the carbonyl component due to the decreased favorability of the reaction at lower pH values. The success of this protocol can be observed by ^{1}H NMR analysis: significant impurity peaks indicate that enolization followed by unwanted side reactions, such as the aldol reaction, have occurred. If there is more than one stereocenter, the observation of epimers would also indicate enolization has occurred. If there are no other stereocenters, optical rotation can be performed to assess the retention of optical purity. Chiral HPLC analysis can be used to determine optical purity if the optical rotation value is unavailable.

This method is extremely facile to perform and to optimize relative to alternate ketone and aldehyde removal protocols. The entire protocol can be performed in less than 15 minutes with common laboratory equipment available in a typical organic chemistry lab. The method is extremely adaptable to novel situations and can be easily adjusted to account for variability in the polarity of substrates of interest. The functional group tolerance is incredibly broad, which makes this protocol applicable to most chemical separations involving a reactive carbonyl component. The protocol can be adapted to mitigate unwanted side reactions caused by the presence of sulfur dioxide generated from bisulfite. Given the prevalence of reactions involving reactive carbonyl compounds in organic chemistry, the ability to quickly and easily remove excess reagents or impurities from mixtures, or re-isolate these materials is extremely valuable. In future, we hope to adapt this protocol to the more challenging purification problem of isolating natural products containing reactive carbonyl compounds from whole organisms.

Disclosures

The authors have nothing to disclose.

Acknowledgements

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