A Novel, Nonaqueous Method for Regeneration of Aldehydes from Bisulfite Adducts

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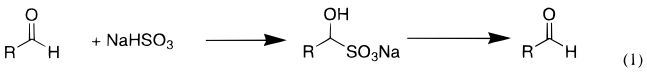
Purification of aldehydes (and cyclic ketones) by crystallization as their bisulfite adducts and then regeneration of the aldehyde is a well-known technique (eq 1).[1]



(1)

Additionally, storage of an aldehyde as the bisulfite adduct gives a significant stability advantage. Yet, the technique appears to be seldom applied. In a search of the Chemical Abstract Services database from 1967 to present we uncovered only 26 papers which describe use of bisulfite adducts in this manner. It is probable that the rarity of the method's use results from two liabilities: (1) bisulfite adducts will not form with hindered aldehydes, (2) the pH extremes required to regenerate the aldehyde are not tolerated by many aldehydes and other functional groups. We report conditions which broaden the utility of the method by addressing the second concern.

The aldehyde **1** is an intermediate in the synthesis of LY231514·2Na,[2] an investigational oncolytic agent.[3] Synthesis of **1** in one step from 4-iodobenzoic acid methyl ester and 3-buten-1-ol has been reported by LaRock (Scheme 1).[4] This method appeared very attractive to us, if the chemoselectivity could be improved. The LaRock coupling method produces a mixture of ca. 90% **1**, 5% **2**, and 5% olefins **3** and **4**. Clearly, the presence of the undesired side products, particularly the isomeric aldehyde **2**, limits the utility of the LaRock method. We were unable to improve the product ratio through optimization of the reaction conditions. Therefore, we sought to develop a commercially viable purification.

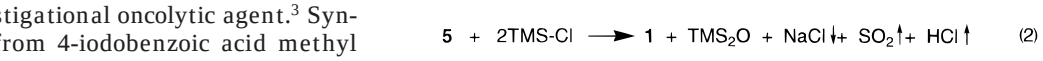
Purification via an intermediate bisulfite adduct **5** appeared attractive. In fact, **5** crystallizes readily when the reaction mixture is treated with sodium bisulfite in a 2:1 (v:v) ethyl acetate:ethanol mixture containing traces of water. Excess sodium bisulfite must be avoided or competitive precipitation of **6** is unavoidable. The desired purity can then be obtained (at the expense of yield) by increasing the water content. At ca. 10% water content (by Karl Fisher titration) approximately 90% of the available **1** can be reproducibly isolated as **5** with less than 0.5% of the isomeric bisulfite adduct **6**. The overall yield for the condensation and bisulfite adduct formation is 75−80%.

The difficulty with this approach became apparent when we began to attempt to regenerate **1** from **5**. The typical approaches found in the literature involve dissolving the bisulfite adduct in water and treating with either acid[5] or base.[6] These conditions increase the equilibrium concentration of aldehyde **1**, which is then either reacted in water or extracted into an organic solvent. We required extraction into an organic solvent for subsequent chemistry. Therefore, we studied extraction of **1** into methylene chloride as a function of pH.[7] These data are presented in Figure 1.

Clearly, high pH is needed for efficient formation and extraction of **1**. However, these conditions carry a liability which is illustrated by Figure 2. If the layers are separated after 3 min, a 97% yield of **1** in the organic phase can be obtained. However, prolonged stirring rapidly consumes **1** and **5** as the ester moiety is hydrolyzed. On a commercial scale at least 30 min would be required which would be expected to result in less than a 50% recovery.

We discovered conditions which avoid ester saponification by elimination of water from the reaction mixture. Treatment of the bisulfite adduct **5** with in excess of 2 equiv of chlorotrimethylsilane (TMS-Cl) in acetonitrile at between 40 and 60 °C rapidly regenerates the aldehyde **1**.

The balanced chemical equation for this reaction is shown below (eq 2). Components in the equation below have been confirmed by ^{1}H NMR and GC analysis of the liquid phase, FT-IR analysis of the gas phase, and ion chromatography of the solid phase.



(2)

In water, a high pH is required to perturb the equilibrium such that **1** is favored. Under the new conditions formation of **1** is irreversible due to the stability of hexamethyldisiloxane, the precipitation of sodium chloride, and the evolution of sulfur dioxide and hydrogen chloride.

For our purposes the mixture of **1** could be used without purification. Several options exist if removal of side-products is required by the next step. Most of the sodium chloride may be removed by filtration. An aqueous washing step will also eliminate the excess TMS-Cl. Addition of a high boiling nonpolar solvent (e.g., toluene), aqueous washing steps, and distillation of the $(TMS)_2O$ provide an aldehyde solution virtually free of side products.

Variations to the above conditions were explored. Acetonitrile was found to be the only acceptable solvent. Reactivity with TMS-Cl eliminates DMSO, alcohols, and DMF from consideration. Reaction in methylene chloride, ethyl acetate, or THF was found to be incomplete after 20 h. Presumably this relates directly to solvent polarity.

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(4) LaRock, R.; Leung, W.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629.
(5) Ehrlich, J.; Bogart, M. T. *J. Org. Chem.* **1947**, *12*, 522.
(6) Cymerman Craig, J.; Hamon D. P. G. *J. Org. Chem.* **1965**, *30*, 4168.
(7) Experiments were conducted on 1.00 g of **1** dissolved in 4 mL of water, pH adjusted with either 4 N HCl or Na_2CO_3, methylene chloride (10 mL), and 3 min agitation. Analysis was by GC.

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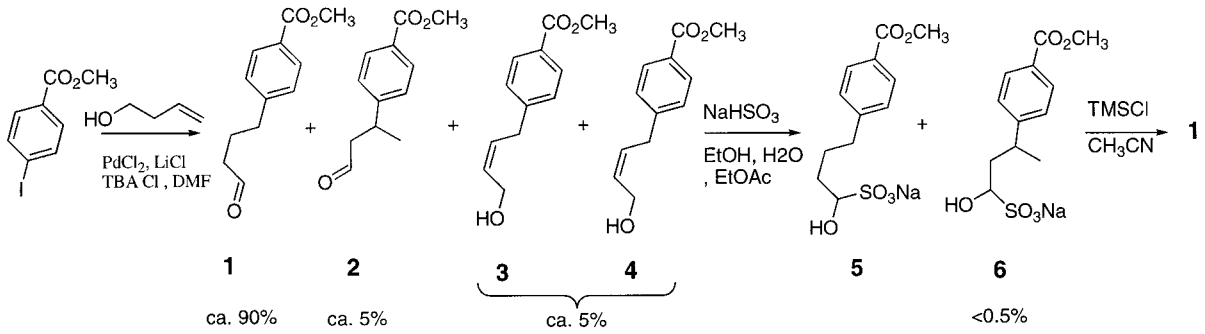
Scheme 1



Other silylating agents were also explored (Table 1). 1-(Trimethylsily)imidazole, *N*,*O*-bis(trimethylsilyl)acetamide, and bis(trimethylsilyl)trifluoroacetamide also produced **1** in quantitative yield. This provides additional flexibility for the method. The more reactive reagents allow reaction at lower temperatures. Also, the side products can be chosen to be compatible with subsequent chemistry. Bromotrimethylsilane and 1,3-bis(trimethylsilyl)urea did not give complete reaction.

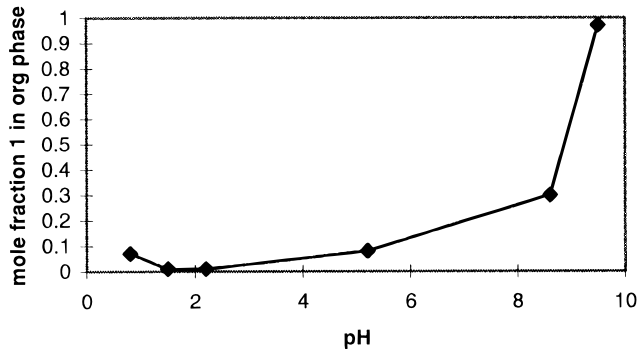


Figure 1. Treatment of 5 in methylene chloride/water at various pH.

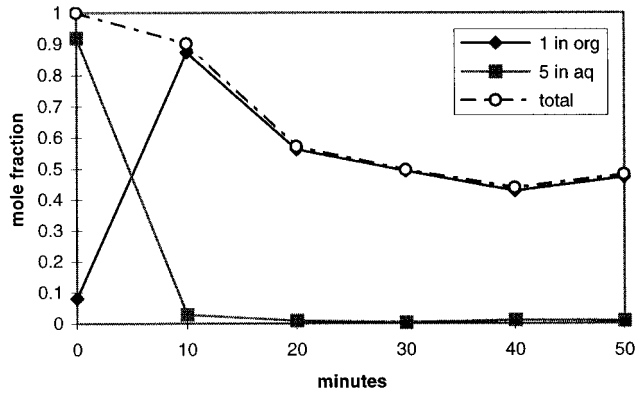


Figure 2. Mole fraction of 1 and 5 in various phases vs time at ambient temperature.

Table 1. Exploration of Alternative Conditions

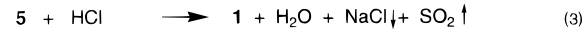
reagent	time (h)	temp (°C)	yield (%)
TMS-Cl	0.5	60	100
TMS-Cl	2	40	100
TMS-Br	2	40	70
TMS-imidazole	12	40	100
1,3-bis(TMS)urea	24	40	20
N,*O*-bis(TMS)acetamide	3	20	100
N,*O*-bis(TMS)trifluoroacetamide	2	0	100
1 equi HCl (g)	2.5	40	0.1
saturated HCl	0.17	40	90
	1		35

Table 2. Purification of Aldehydes via Bisulfite Adducts

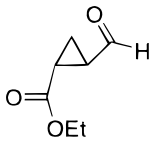
substrate		bisulfite adduct		regenerated aldehyde (in situ or isolated)	
structure	initial purity (%)	yield (%)	purity[a] (%)	yield[b] (%)	purity[c] (%)
7	88[d]	61 (**7-A**)	>98	98	>99
8	90[e]	95 (**8-A**)	>99	*>95*	*>99*
9	90+[e]	79 (**9-A**)	>99	*>95*	*>95*
10	90[e]	52 (**10-A**)	96	*>95*	*>95*

[a] Estimated from ^{1}H NMR integration of hydroxyl protons of main compound and any impurities. [b] For in situ analysis yield was estimated from ^{1}H NMR integration of well separated peaks vs an internal standard (either pyrazine or anisole). [c] Purity was estimated from ^{1}H NMR integration of aldehyde protons of main compound and any impurities. [d] By ^{1}H NMR integration of major peaks for trans isomer vs minor (cis) isomer. [e] From manufacturers label.

Reaction of **5** with gaseous HCl was also investigated. No reaction was observed with 1 equiv of HCl (g). This clarifies the mechanism of the TMS-Cl reaction; the HCl generated is not the true active species. However, when the acetonitrile solution of **5** is saturated with HCl at 40 °C, deblocking occurs rapidly. A 90% in situ yield of **1** was obtained in 10 min. Product instability precludes large scale operation with these conditions; the in situ yield was reduced to 35% after 1 h. The product instability under these conditions is expected since water is a product under these conditions (eq 3).



Utility was demonstrated on multiple substrates. Commercially available, impure aldehydes were chosen for study. For these experiments water content was fixed at ca. 10%, and the sodium bisulfite stoichiometry was reduced until purity was optimized. The results of these studies are shown in Table 2. Ethyl 2-formyl-1-cyclopropanecarboxylate **7** is representative. Compound **7** is commercially available as a "predominately trans" mixture. We estimate by ^{1}H NMR that the mixture was 88:12, trans:cis. The bisulfite adduct easily formed in an unoptimized yield of 61%. Cis contamination was barely detectable. Regeneration of **7** was essentially quantitative, both in situ (by ^{1}H NMR integration with an internal standard) and after isolation. Hydrocinnamaldehyde **8** and phenylacetaldehyde **9** were easily isolated as pure bisulfite adducts and regenerated as pure solutions. An interesting example is 2,2-dichlorohexanal **10**. This compound is very hygroscopic, so obviously a typical aqueous procedure for bisulfite cleavage would fail. Formation of the bisulfite adduct **10-A** required a low yield for good purity under these unoptimized conditions. However, regeneration of **10** was uneventful.



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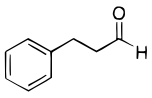

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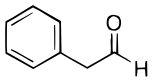

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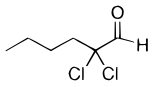

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In summary, a new method for cleavage of bisulfite adducts to the parent aldehydes has been developed. The new method is nonaqueous, which greatly expands the list of aldehydes which are compatible. Utility has been demonstrated by the purification of **1** generated by the LaRock coupling procedure and by the purification of commerically available aldehydes **7**−**10**.

Experimental Section

Analytical instrumentation was as previously described.[8] Ethyl 2-formyl-1-cyclopropanecarboxylate **7** (Aldrich), hydrocinnamaldehyde **8** (Aldrich), phenylacetaldehyde **9** (Aldrich), and 2,2-dichlorohexanal (Acros), all reagents, and all solvents were used as obtained. All reactions were run under a nitrogen atmosphere.

General Procedure for Bisulfite Adduct Formation. The synthesis of ethyl 2-formyl-1-cyclopropanecarboxylate bisulfite adduct **7-A** is representative.[9] Aldehyde **7** (2.0 g, 14.1 mmol), sodium bisulfite (1.31.g, 12.6 mmol), ethyl acetate (10 mL), ethanol (6 mL), and water (2 mL) were combined and heated to 40 °C for 2.2 h. The mixture was allowed to cool to ambient temperature, filtered, washed with ethanol (10 mL), and dried to give bisulfite adduct **7-A** as colorless crystals (2.11 g, 8.6 mmol, 61%).

4-(4-Carbomethoxyphenyl)butanal Bisulfite Adduct (5). A mixture of compounds **1**−**4** in DMF was prepared as previously described.[4] Addition of ethyl acetate, and filtration, followed by aqueous and brine washes, yielded a solution in ethyl acetate ready for bisulfite adduct formation by the standard method. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.33 (d, J = 5.7 Hz, 1H), 3.82−3.87 (m, 1H), 3.81 (s, 3H), 2.58−2.67 (m, 2H), 1.36−1.84 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 166.23, 148.32, 129.17, 128.69, 127.10, 82.69, 51.94, 35.06, 31.25, 27.16.

Ethyl 2-Formyl-1-cyclopropanecarboxylate Bisulfite Adduct (7-A). ^{1}H NMR (DMSO-d_6) δ 5.58 (d, J = 5.9 Hz, 1H), 3.93−4.11 (m, 2H), 3.50−3.57 (m, 1H), 1.59−1.68 (m, 2H), 1.16 (t, J = 7.0 Hz, 3H), 0.89−0.98 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 173.47, 83.04, 59.75, 23.87, 16.80, 14.07, 12.65.

Hydrocinnamaldehyde Bisulfite Adduct (8-A). ^{1}H NMR (DMSO-d_6) δ 7.12−7.31 (m, 5H), 5.37 (br, 1H), 3.82 (d, J = 9.2 Hz, 1H), 2.70−2.81, m, 1H), 2.54−2.66 (m, 1H), 1.97−2.97 (m, 1H), 1.68−1.82 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 142.21, 128.32, 128.15, 125.50, 33.71, 31.47.

Phenylacetaldehyde Bisulfite Adduct (9-A). Mp > 300 (dec); ^{1} H NMR (DMSO-d_6) δ 7.12−7.30 (m, 5H), 5.42 (br, 1H), 4.02 (dd, J = 4.0, 11.0 Hz, 1H), 3.14 (dd, J = 2.0, 13.8 Hz, 1H), 2.70 (d, J = 10.5 Hz, 1H), 2.65 (d, J = 10.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 139.7, 129.21, 127.88, 125.64, 84.06, 38.06. Anal. Calcd for $C_8H_9O_4SNa$ (224.01): C, 42.86; H, 4.05.

2,2-Dichlorohexanal Bisulfite Adduct (10-A). ^{1}H NMR (DMSO-d_6) 6.22 (d, J = 6.9 Hz, 1H), 4.28 (d, J = 6.9 Hz, 1H), 2.42−2.51 (m, 2H), 1.53−1.71 (m, 2H), 1.24−1.38 (m, 2H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 97.67, 89.03, 42.59, 27.44, 22.21, 14.30.

General Procedure for Regeneration of Aldehydes from Bisulfite Adducts. Regeneration of ethyl 2-formyl-1-cyclopropanecarboxylate **7** is representative. Ethyl 2-formyl-1-cyclopropanecarboxylate bisulfite adduct **7-A** (1.00 g, 406 mmol), CD_3CN (8.0 mL), anisole or pyrazine(as an internal standard for analysis), and TMS-Cl (1.22 g, 11.2 mmol) were combined and heated to 40 °C. After 2.2, h ^{1}H NMR analysis of filtered aliquots indicated a quantitative in situ yield of **7**. The mixture was allowed to cool to ambient temperature. Ethyl acetate (6.0 mL) was added. The mixture was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield **7** (0.511 g, 3.6 mmol, 98% (corrected for sampling losses)).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for bisulfite adducts **5**, and **7A** through **10A**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990543V

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