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A Practical, Efficient Synthesis of 1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-carbaldehyde

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Abstract:

A practical, efficient, and scalable procedure for the preparation of 1,1-dioxo-hexahydro-1λ^6-thiopyran-4-carbaldehyde is reported. Synthesis of this aldehyde was complicated by high aqueous solubility of the product and the intermediates. The isolation and purification of the aldehyde was accomplished by conversion to the crystalline bisulfite adduct.

Introduction

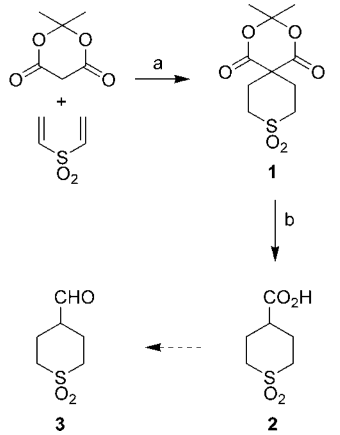
A recent project in our group required 1,1-dioxo-hexahydro-1λ^6-thiopyran-4-carbaldehyde **3** as a key intermediate in the synthesis of a biologically active target molecule. To our knowledge, there is no synthesis of **3** reported in the literature; however, the related carboxylic acid **2** has been obtained in 29% yield for a two-step process from Meldrum's acid and divinylsulfone.[1] Carboxylic acid **2** seemed a reasonable and readily accessible intermediate by which to obtain the desired aldehyde. As such, our efforts initiated with an evaluation of the reported synthesis of **2**.

Carboxylic acid **2** is formed by the base-catalyzed double Michael addition of Meldrum's acid to divinylsulfone followed by hydrolysis and decarboxylation. The Meldrum's adduct **1** was prepared by treatment of a *tert*-butanol solution of divinylsulfone and Meldrum's acid with 10 mol % solid potassium hydroxide at 80 °C. While the 68% yield reported was reproduced on small scale, the yield dropped dramatically on scaling. The decrease in yield upon scaling could be attributed to two separate issues: the method of agitation and the stability of Meldrum's acid to the reaction conditions.

On larger scale, the magnetic stir bar, which physically ground up the solid KOH pellets in the reaction flask, was replaced with overhead stirring. Replacing KOH pellets with granular K_2CO_3 or soluble organic bases such as 1,8-diazabicyclo[5.4.0]undecane, diisopropylethylamine, or potassium *tert*-butoxide resulted in consistent reaction performance regardless of the choice of agitation.

Upon scale-up from bench scale (100 mmol) to pilot scale (>10 mol), a sharp decrease in yield was observed. The original reaction procedure involved charging all of the reagents to the reactor and heating the mixture to reaction temperature. The most likely cause for this decrease in yield was the longer times required for heating the reaction to temperature. Indeed, when the divinylsulfone, Meldrum's acid, and K_2CO_3 are combined in *tert*-butanol and heated to 80 °C in 30 min, the reaction yield was >90%. If the time to heat the reaction from room temperature to 80 °C was increased to 120 min, the yield decreased to 57%. The decrease in yield was attributed to the decomposition of Meldrum's acid in the presence of base which takes place well below the temperature required to promote the desired Michael addition. This issue was addressed by charging the Meldrum's acid portionwise to the mixture of *tert*-butanol, K_2CO_3, and divinylsulfone at 80 °C. Performing the reaction with these two modifications—change in base and order of addition—the 85−90% yield for **1** was obtained on 5-kg scale. Upon cooling the crystalline Meldrum's adduct, **1** was isolated from the reaction by filtration with adequate purity for direct use in the next step.

Scheme 1[a]



[a] Reagents and conditions: (a) K_2CO_3, *t*-BuOH, 80 °C. (b) 6 N HCl, 100 °C.

The reported procedure for hydrolysis and decarboxylation of **1** to obtain the carboxylic acid **2** consisted of heating **1** in dilute aqueous sulfuric acid followed by extraction with ethyl acetate to give a 42% yield of carboxylic acid **2**.[2] The low yield of **2** was likely due to losses to aqueous during isolation; indeed the high water solubility of these functionalized thiopyrans was a problem repeatedly encountered during the development of a route to **3** (see Scheme 1). Hoping to limit the amount of water in this reaction to aid extraction efficiency, **1** was slurried in

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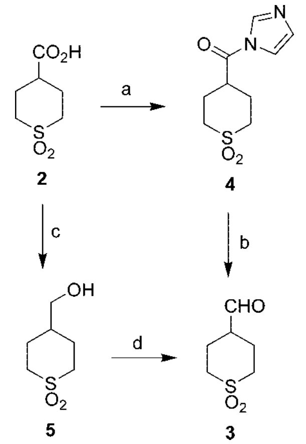
[1] (a) Carlon, E.; Draper, R. W.; Friary, R. *Org. Prep. Proced. Int.* **1977**, *9*, 94–96. A longer and far less efficient synthesis of **2** is also known: (b) Cockburn, W. F.; McKay, A. F. *J. Am. Chem. Soc.* **1954**, *76*, 5703. While the aldehyde has appeared as a reagent in a few published articles, we have not found a reported synthesis.

[2] The diacid is an observed intermediate in this reaction, suggesting that a simple hydrolysis−decarboxylation mechanism is operative as opposed to a plausible pathway to **2** via ketene.

10.1021/op800108s CCC: $40.75

Scheme 2[a]



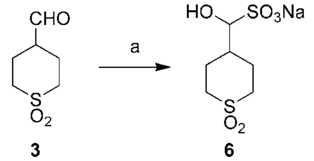
[a] Reagents and conditions: (a) CDI, THF, RT. (b) DIBAL-H, THF, −30 °C. (c) $BH_3 \cdot SMe_2$, CH_2Cl_2, 35 °C. (d) $SO_3 \cdot$pyridine, DMSO, Et_3N, CH_2Cl_2.

approximately three volumes[3] of 6 N HCl and heated to 100 °C to effect conversion to **2**. While the reaction is homogeneous at 100 °C, upon cooling **2** crystallized from the concentrated acid solution in high purity and in 65% overall yield from divinylsulfone. The literature two-step procedure had reported only 28%.

With an efficient route to carboxylic acid **2**, methods for conversion to the desired aldehyde **3** were investigated. The initial approach was to reduce the imidazole adduct **4** with diisobutylaluminum hydride (DIBAL-H) to afford the aldehyde directly. Treatment of **1** with 1,1′-carbonyldiimidazole (CDI) followed by addition of excess DIBAL-H with the reaction at −30 °C gave the desired aldehyde along with the over-reduced product, alcohol **5** (see Scheme 2). Alternatively, the imidazolide **4** could be isolated as a crystalline solid from THF−MtBE in 96% yield. Reduction of isolated **4** to aldehyde **3** required less DIBAL-H than the through-process but still resulted in partial over-reduction. The formation of **5** could be suppressed by lowering the temperature to −70 °C, but this was deemed impractical for scalable production of **3**. Furthermore, the high water solubility of the resulting aldehyde made removal of the aluminum salts and isolation of pure aldehyde a significant challenge.

Since the over-reduction of the aldehyde was difficult to control, a two-step reduction−oxidation approach was pursued. Reduction of **2** with $BH_3 \cdot THF$ in THF gave **5** as a crystalline solid, but the poor solubility of both **2** and product **5** in THF led to the formation of gummy solids during the course of the reaction which compromised reaction performance and complicated isolation and purification. This problem was avoided by performing the reaction in dichloromethane with neat $BH_3 \cdot SMe_2$ at 35 °C which afforded a homogeneous end-of-reaction solution and consistently high conversion. A typical extractive aqueous workup to remove boronic acid byproducts resulted in very low recovery of **5**, again due to its high water solubility (>300 mg/mL). Alternatively, quenching the reaction at 35 °C with one equivalent of potassium fluoride as a 50 wt % solution in water removed most of the boronic acid byproducts with minimal loss of alcohol to the resulting aqueous phase. The dichloromethane solution of **5** was then concentrated to low volume and *tert*-butyl methyl ether added to crystallize the alcohol in 86% isolated yield.[4]

Scheme 3[a]



[a] Reagents and conditions: (a) $NaHSO_3$, EtOH, H_2O, 50 °C.

While a variety of conditions were screened, the oxidation of **5** to aldehyde **3** was found to be best by using the conditions of Parikh and Doering.[5] Treatment of a dichloromethane solution of **5** with 2.5 equiv of DMSO, 2 equiv of triethylamine, and then portion-wise addition of 1.5 equiv of solid sulfur trioxide pyridine complex at 0 °C gave the desired aldehyde in 85% assay yield. The remaining challenge was isolation−purification of the aldehyde from reaction solution. Due to the significant water solubility of **3** (>300 mg/mL), a low-volume, highly ionic aqueous HCl workup to remove the reagent byproducts was used. Although the solution of aldehyde obtained at this point could be used for most purposes, a means to isolate this key intermediate as a crystalline compound was desired in order to control its purity.[6]

Robust purification and isolation of the aldehyde from the oxidation stream was accomplished via formation of its bisulfite adduct **6**. Following workup the dichloromethane solution of aldehyde was concentrated to a low volume and then treated with sodium bisulfite, water, and finally ethanol at 50 °C[7] (see Scheme 3). Upon cooling, the bisulfite adduct **6** was isolated as a crystalline solid in 76% overall yield from alcohol **5**. For applications such as reductive amination the direct use of aldehyde bisulfite adducts have been reported, obviating the need to regenerate the aldehyde.[8] For our particular application the direct use of **7** was not practical, and a route to free aldehyde **3** was required.

Typically an aldehyde can be recovered from its bisulfite adduct by treatment with aqueous acid and extraction of the aldehyde with organic solvent.[9] The reactivity and water solubility of aldehyde **3** was such that upon treatment with acid only trace amounts of aldehyde could be extracted into organic

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(3) Volumes here is used according to the convention: mL of 6 N HCl/g of **1**.

(4) The CH_2Cl_2 solution of **5** obtained can be used directly in the oxidation step with no change in reaction performance.

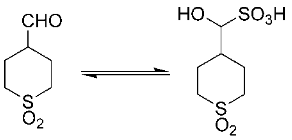
(5) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(6) Crystallization of the aldehyde following oxidation was complicated by the pyridine, DMSO, and oxidation byproducts.

(7) Order addition proved important here. Addition of ethanol prior to water led to the formation of the diethylacetal from which the aldehyde could only be recovered by hydrolysis with aqueous acid.

(8) A reductive amination directly with an aldehyde bisulfite adduct was demonstrated: Ragan, J. A.; am Ende, D. J.; Brenek, S. J.; Eisenbeis, S. A.; Singer, R. A. , Tickner, D. L.; Teixeira, J. J., Jr.; Vanderplas, B. C.; Weston, N. *Org. Process Res. Dev.* **2003**, *7*, 155−160.

(9) Jencks, W. P.; Young, P. R. *J. Am. Chem. Soc.* **1978**, *100*, 1228–1235.



3 7

Figure 1.

solvent.[10] The equilibrium between **3** and **7** in aqueous acid appears to heavily favor the bisulfite adduct **7** (Figure 1.). A THF solution of the aldehyde−bisulfite could be obtained by treatment of a slurry of **6** in THF with one equivalent of concd HCl and heating to 50 °C for 1 h. At the end of the reaction, the precipitated salt (presumably sodium chloride) was filtered and the solution dried by azeotropic distillation of THF. Interestingly, the aldehyde solutions obtained in this fashion did not function well in reductive aminations, possibly due to inhibition by the sulfinic acid also present in the solution. The aldehyde **3** could be isolated as a crystalline solid by addition of *tert*-butyl methyl ether to a dry, concentrated THF solution of aldehyde. Unfortunately the product was isolated with variable levels of an impurity which was characterized as a polymeric form of the aldehyde. Furthermore, the amount of polymer increased substantially on storage of the crystalline aldehyde and could not be converted back to free aldehyde under useful conditions. While in most cases the amount of polymer accounted for <10 mol % total aldehyde, the variability observed in product purity and the instability to storage led us to investigate a base-mediated break of the bisulfite.[11]

We were pleased to observe that the equilibrium which favored bisulfite adduct **7** in acidic aqueous solution was evidently not operative with respect to the bisulfite adduct **6** present in basic systems. The aldehyde could be efficiently recovered by dissolution of **6** in 0.95 equiv of 2 N aqueous sodium hydroxide followed by extraction with dichloromethane. The aldehyde was isolated as a white crystalline solid by concentration of the dichloromethane solution and addition of *tert*-butyl methyl ether anti solvent. Aldehyde, prepared in this manner, contained none of the undesired polymer and was obtained in >80% yield from bisulfite **6**.

A practical and scalable synthesis of sulfone aldehyde **3** has been achieved, overcoming the significant water solubility and reactivity issues unique to this aldehyde. The described synthetic route provides practical access to the target carboxaldehyde **3** in four steps with 48% overall yield from divinylsulfone and with adequate purity for most applications.[12] In order to provide **3** with purity requisite of a late-stage pharmaceutical intermediate, the convenient isolation and purification via bisulfite adduct **6** was developed. Finally, the efficient synthetic route to **3** also provides access to the potentially useful synthetic building blocks: Meldrum's adduct **1**, carboxylic acid **2**, and alcohol **5**.

Experimental Section

General. All reactions were conducted under N$_2$ atmosphere using standard air-free manipulation techniques. Solvents and common reagents were purchased from commercial source and used without further purification. Concentration *in vacuo* refers to removal of the solvent at reduced pressure. All new compounds are characterized below. While this chemistry has been performed on multikilogram scale, the conditions below describe conditions further optimized following a pilot-plant campaign.

3,3-Dimethyl-2,4-dioxa-9-thiaspiro[5.5]undecane-1,5-dione-9,9-dioxide (1). Divinylsulfone (5.89 g, 49.8 mmol) was charged to refluxing *tert*-butanol (80 °C, 100 mL, 1070 mmol) followed by addition of K$_2$CO$_3$ (1.72 g, 12.5 mmol, reagent grade powder, −325 mesh). 2,2-Dimethyl-1,3-dioxane-4,6-dione (8.60 g, 59.8 mmol) was added in five portions over 30 min to the reaction solution at 80 °C. The reaction was stirred at 80 °C for 1 h or until HPLC showed complete consumption of the divinylsulfone.[13] The reaction was cooled to 35 °C, and MtBE (20.0 mL, 168 mmol) was added. The slurry was stirred at 35 °C for 12 h and then filtered; the cake was dried in a vacuum oven at 60 °C, with N$_2$ bleed, overnight. The desired adduct **1** was isolated as a white solid in near quantitative yield (13.0 g, 496 mol, >98% yield). ^{1}H NMR of **1** was consistent with that reported in the literature for this compound.[1]

Thian-4-carboxylic Acid 1,1-Dioxide (2). 3,3-Dimethyl-2,4-dioxa-9-thiaspiro[5.5]undecane-1,5-dione-9,9-dioxide **1** (20.0 g, 76.3 mmol) and then 6 N hydrochloric acid (60 mL) and Antifoam 204 (200 mg, 1 wt % relative to **1**) were charged to a 250-mL, three-neck round-bottom flask, equipped with a mechanical stirrer and a thermocouple.[14] The reaction was then heated to reflux and distillate collected until the internal temperature reached 100 °C; thereafter the reaction was allowed to reflux for an additional 8 h or until LC/MS showed complete conversion of **1** to **2**.[15] The reaction was then cooled to room temperature and held for ~12 h, during which time the product crystallized from solution. The slurry was cooled to 0 °C for 1 h and then filtered. The cake was dried in vacuum oven at 60 °C, with nitrogen bleed, overnight to give **2** as a white, crystalline solid (8.84 g, 49.6 mmol, 65% yield, >98 wt % by quantitative ^{1}H NMR vs benzyl benzoate standard). ^{1}H NMR of **2** was consistent with that reported in the literature for this compound.[1]

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(10) A non-aqueous method for regeneration of aldehydes from bisulfite adducts has been reported: Kjell, D. P.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64*, 5722–5724, While this method was successful for regenerating aldehyde **3**, it was ultimately not used due to the acidic nature of the conditions which complicated isolation of our aldehyde *(vide infra)*.

(11) The polymerization is most likely an acid-catalyzed process and variable due to variable amounts of acid present during the crystallization and in the resulting solid. That no polymer is observed in aldehyde isolated under basic conditions supports this conclusion.

(12) Yield calculated to the CH$_2$Cl$_2$ solution of aldehyde obtained out of the oxidation step. For many applications this solution of aldehyde can be used directly. Alternatively, the bisulfite adduct is obtained in 42% overall yield, and the crystalline aldehyde may be recovered from bisulfite with 35% overall yield from divinylsulfone.

(13) Reaction progress was monitored by divinylsulfone disappearance observed by HPLC at 210 nm with retention time = 2.55 min. on an Eclipse XDB C-8 4.6 mm × 150 mm, 5 μm column at 35 °C, eluting with 0.1% HClO$_4$ aqueous and MeCN at 1.5 mL/min. with a gradient of 10% MeCN to 70% MeCN over 7 min.

(14) Antifoam 204 is a Sigma-Aldrich product. It was used to suppress foaming during the decarboxylation reaction.

(15) Reaction progress was monitored by LC/MS fitted Zorbax SB-C8 4.6 mm × 75 mm, 3.5 μm column eluted at 1 mL/min with water and MeCN each containing 0.1% AcOH on a gradient of 10% MeCN to 90% MeCN over 9 min. The starting material **1** is detected at 4.11 min and the product **2** at 1.49 min by evaporative light scattering detector at 40 °C. During the course of the reaction **1** is rapidly hydrolyzed to the corresponding diacid which is then slowly converted to **2** as observed by LC/MS.

(1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-yl)methanol (5). Neat $BH_3 \cdot SMe_2$ was added (~10 M, 33.7 mL, 337 mmol, 1.2 equiv) over 30 min to a slurry of **2** (50 g, 280.5 mmol) in 500 mL of CH_2Cl_2 at 37 °C. (**Caution! Hydrogen Gas Evolution!**) The slurry was stirred 1.5 h at 37 °C until GC assay indicated complete conversion of **2** to **5**.[16] With the reaction at 37 °C, an aqueous solution of KF (19.6 g in 40 mL of water, 337 mmol, 1.2 equiv) was added over 45 min. (**Caution! Hydrogen Gas Evolution!**) The biphasic mixture was then stirred at 37 °C for 2 h and then cooled to 30 °C; the bottom aqueous layer was then cut and discarded. The organic phase was concentrated by atmospheric distillation to low volume (approximately 80−100 mL total volume), and then 400 mL of MtBE was added slowly to effect crystallization of **5**. The slurry was cooled to 0 °C and filtered, washing the cake with 2 × 50 mL of MtBE. The solids were dried overnight in a 60 °C vacuum oven with N_2 bleed. Alcohol **5** was isolated as a white solid in 86% yield (39.52 g, 241 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, 2H), 3.08 (d, 2H), 2.96 (m, 2H), 2.19 (d, 2H), 1.86 (m, 3H), 1.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.8, 50.8, 37.8, 26.7. HRMS calcd for $C_6H_{12}O_3S$ [M + H] 165.05799. Found 165.05791.

(1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-yl)-hydroxy-methanesulfonic Acid, Sodium Salt (6). Sulfur trioxide pyridine complex (57.0 g, 358 mmol, 1.5 equiv) was added in five portions over 1 h to a solution of **5** (39.24 g, 239 mmol), DMSO (42.4 mL, 598 mmol, 2.5 equiv), and Et_3N (66.6 mL, 478 mmol, 2.0 equiv) in 395 mL of CH_2Cl_2 at 0−10 °C. The solution was stirred 30 min at >10 °C and then 2 h at room temperature until GC assay showed complete conversion of **5**. The solution was then cooled to 0 °C, and HCl (concd HCl aq, 60 mL, 717 mmol, 3.0 equiv) was added while allowing the temperature to rise to 20 °C during addition. The aqueous portion was extracted two more times with 100 mL of CH_2Cl_2 each, and the combined organic extracts were concentrated by atmospheric distillation to 130 mL total volume. Water (39 mL), Na_2SO_3 (25 g, 236 mmol), and then EtOH (315 mL) were added, the slurry was heated at 50 °C for 4 h[17] and then cooled to room temperature, and the mixture was stirred overnight. The slurry was filtered, and solids were washed with EtOH and dried under N_2 to give **6** (48.6 g, 182.5 mmol) as a white solid in 76% yield from **5**. ^{1}H NMR (400 MHz, D_2O) δ 4.43 (d, 1H), 3.33 (m, 4H), 2.53 (m, 1H), 2.32 (m, 2H), 2.10 (m, 2H). ^{13}C NMR (100 MHz, D_2O with MeOH internal standard at 49.5 ppm) δ 86.1, 50.6, 50.4, 37.0, 28.0, 24.7. HRMS calcd for $C_6H_{11}NaO_6S_2$ [M + Na] 288.97870. Found 288.97808.

1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-carbaldehyde (3). Sodium hydroxide (2 N aq 17.8 mL, 35.7 mmol, 0.95 equiv) was added to a slurry of **6** (10 g, 37.6 mmol) in 50 mL of CH_2Cl_2 at 20 °C.[18] The biphasic mixture was stirred rapidly for 2 h, and then the organic phase was cut and retained. The aqueous was extracted with 2 × 50 mL of dichloromethane, and the organic extracts were combined and concentrated *in vacuo* to 20 mL total volume which assayed for 83% yield of the desired aldehyde **3**, (5.12 g, 31.6 mmol). The aldehyde solution was typically used as is but may be crystallized as follows: the solution of **3** was concentrated to ~10 mL, and then seed crystals of aldehyde were added along with 10 mL of MtBE. A seed-bed developed over 30 min, and then a further 80 mL of MtBE was added slowly. Filtration and drying at ambient under a N_2 provided **3** as a white crystalline solid, stable at ambient conditions for >6 months.[19] ^{1}H NMR (400 MHz, D_2O) δ 9.61 (s, 1H), 2.99 (m, 4H), 2.51 (m, 1H), 2.35 (m, 2H), 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 49.7, 45.7, 23.6. HRMS calcd for $C_6H_{10}O_3S$ [M + H] 163.04234. Found 163.04271.

(1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-yl)-imidazol-1-yl-methanone (4). 1,1-Carbonyldiimidazole (9.4 g, 57.9 mmol, 1.2 equiv) was charge in one portion to a 250-mL, three-neck flask containing carboxylic acid **2** (8.6 g, 48.3 mmol, 1 equiv) as a slurry in 60 mL of tetrahydrofuran. (**Caution! Rapid Gas Evolution!**) Reaction was stirred for 1 h at room temperature by which time gas evolution had stopped, and a white slurry was obtained. MtBE (43 mL) was added over 30 min, the reaction was aged 1 h, the slurry was filtered and rinsed with MtBE, and the cake was dried under N_2 stream to give 11.1 g of **4** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 7.75 (s, 1H), 7.12 (s, 1H), 3.61 (m, 1H), 3.28 (m, 2H), 3.19 (m, 2H), 2.30 (m, 2H), 2.10 (m, 2H).

Supporting Information Available

Representative NMR spectra for compounds **2**, **3**, **4**, **5** and **6**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(16) The aldehyde **3**, alcohol **5** and carboxylic acid **2** were analyzed by GC using the following method. HP-5 column at 100 °C initial temp, ramp to 325 at 25 °C per min., constant flow = 1.3 mL/min., split ratio = 10:1, hydrogen as carrier gas, retention times: **3** = 4.31, **5** = 4.95, **2** = 5.32 min.

(17) Conversion of the aldehyde to bisulfite is apparent as a change in the quality of the slurry. The conversion can be quantified by GC analysis of the supernatant to observe disappearance of the aldehyde. The bisulfite adduct is not observed in the GC and does not appreciably thermally revert to aldehyde on GC injector port if the temperature is kept at 150 °C. Alternatively *in situ* IR or ^{1}H NMR may be used to monitor conversion.

(18) No products arising from decomposition of CH_2Cl_2 by NaOH are observed following this procedure as a result of the deliberate undercharge of dilute NaOH to ensure that all is converted to Na_2SO_3.

(19) This crystalline aldehdyde appears to form solvates readily. On isolation from MtBE−CH_2Cl_2 it retains about 9 wt % solvent by NMR. Following purification by flash chromatography on silica gel with 30% acetone−CH_2Cl_2 the isolated crystalline solid retains acetone and CH_2Cl_2 after extended drying under dry nitrogen. The stability of the aldehyde isolated from the basic bisulfite break described is in stark contrast to the rapid decomposition observed for crystalline aldehyde isolated from acidic bisulfite break procedures which often decomposed >30% in a matter of days at ambient temperature.