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# Synthesis of alkyl sulfonic acid aldehydes and alcohols, putative precursors to important wine aroma thiols

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ABSTRACT

The synthesis of the low molecular weight sulfonic acids, 2-methyl-4-oxopentane-2-sulfonic acid, 1-hydroxyhexane-3-sulfonic acid, 1-oxohexane-3-sulfonic acid and 1-hydroxyhexane-1,3-disulfonic acid from *trans*-2-hexenal and ethyl hex-2-enoate is reported. These sulfonic acids are putative precursors to the important wine aroma thiols, 3-mercaptohexan-1-ol, 3-mercaptohexyl acetate and 4-mercapto-4-methylpentan-2-one.



Wine aroma is the culmination of the interactions between the grape and yeast metabolome, comprising of a great number of metabolites.[1] One group of these well-known aroma compounds, that has risen to prominence, consists of the volatile thiols: 3-mercaptohexan-1-ol (3MH), 3-mercaptohexyl acetate (3MHA) and 4-mercapto-4-methylpentan-2-one (4MMP) (Fig. 1).[2] These compounds are present in very low concentrations in certain wines, and have an extremely low sensory threshold,[3] imparting strong favourable characteristics to wine aroma.[4] It is therefore of considerable interest to know how these compounds are formed so that attempts can be made to maximise their concentrations in wine.

As these thiols are not present in grape juice,[5] it follows they are formed from precursors at some stage during the wine-making process. Whilst it has been established that the non-volatile *S*-cysteinyl (Cys-3MH, Cys-4MMP) and *S*-glutathionyl adducts (GSH-3MH, GSH-4MMP) (Fig. 1), which are present in grape juice, are metabolised into the thiols in question,[6,7] it remains unclear as to whether these are the only precursors. It has been found that conversion of Cys-3MH and GSH-3MH into 3MH accounts for as little as 1% of total 3MH,[6b,8] and higher concentrations of Cys-3MH and GSH-3MH do not consistently result in higher concentrations of the free thiols,[8] with the same scenario for 4MMP and its precursors.[7a] These results indicate the strong possibility that other important aroma thiol precursors might exist.[9]

One hypothesis is that structurally related sulfonic acids are possible precursors to the thiols of interest. Previous studies have shown that α,β-unsaturated compounds, including mesityl oxide,[10] in the presence of bisulfite, form several sulfonic acid products (Fig. 2),[11] some of which show obvious chemical analogy to the aroma thiols. *trans*-Hex-2-enal occurs naturally in small (in the range of 0.2–1 parts per billion)[12] amounts in grape juice and wine,[13] whilst mesityl oxide hydrate has been identified in wine in the range of parts per billion concentration, and has also been identified in some species of grape.[14] Potassium metabisulfite, in concentrations in the range of parts per million, is added by wine-makers during the wine-making process for its antioxidant activity and is hence in large excess when compared to the natural α,β-unsaturated compounds.[15,16] It is reasonable to assume that the sulfonic acids shown in Figure 2 could therefore be formed during wine production. The chemical similarity between 3MH and its sulfonic acid analogue raises the interesting possibility that sulfonic acids may be reduced by yeast to their corresponding free thiols. In order to explore this hypothesis, pure samples of the sulfonic acids **1**–**4** are required. However, there are few examples of compounds of this type being prepared, whilst previous work also lacks detail and contains conflicting information.[10,11]

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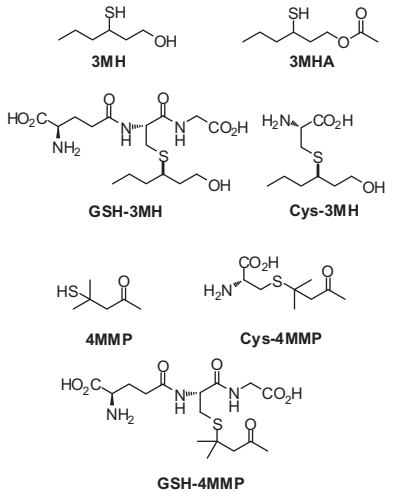



**Figure 1.** Known aroma thiols and precursors.

The 4MMP sulfonic acid analogue **1** was synthesised by adapting a previous method,[10b] using a mixture of mesityl oxide, sodium metabisulfite and triethylamine (Scheme 1). It was found that rapid purification using an ion exchange resin was required or formation of the difficult to purify sulfonic acid triethylamine salt was favoured. Purification was therefore undertaken immediately following work-up of the reaction and gave the desired sulfonic acid **1** in 62% yield.[17]

Previous studies have reported that isolating sulfonic acid aldehydes, such as **4**, have proven problematic.[11c,18] It was therefore decided to attempt bisulfite addition to *trans*-ethyl hex-2-enoate (**6**) rather than *trans*-hex-2-enal. This would stop competing 1,2-addition, as well as the known oxidation of the aldehyde to the acid. Ester **6** was prepared via Wittig reaction of butanal with (carbethoxymethylene)triphenylphosphorane giving ester **6** in 72% yield (Scheme 2).[19] Ester **6** was reacted with 1.1 equiv of aqueous sodium bisulfite, which unexpectedly gave acid **7** as the major product, along with a lesser amount of ester **8**, showing that standard conditions for bisulfite addition also result in ester hydrolysis.[20] Unfortunately, both acid **7** and ester **8** were particularly resistant to reduction, and both required refluxing with excess of lithium aluminium hydride in THF. These conditions gave mixtures of the sulfonic acid alcohol **2** and a sulfonate-tetrahydrofuran chelate, in quantitative yield. Acidification of the product mixture failed to remove the chelated THF, as did purification using an ion exchange resin. However, it was found that with careful column chromatography using methanol/acetic acid (99:1) the desired alcohol **2** could be obtained in 80% yield from ester **8**,[21] with a lower 12% yield of **2** being obtained from the reduction of acid **7**.

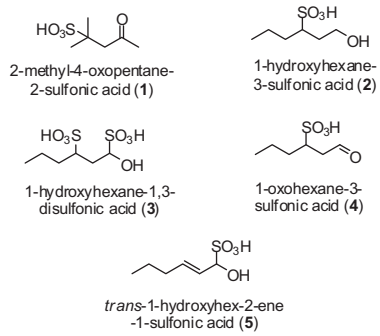
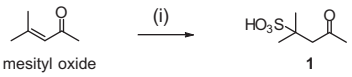
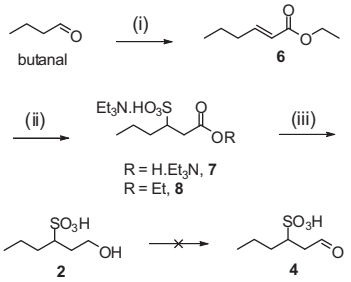



**Figure 2.** Sulfonic acids **1**–**5**.



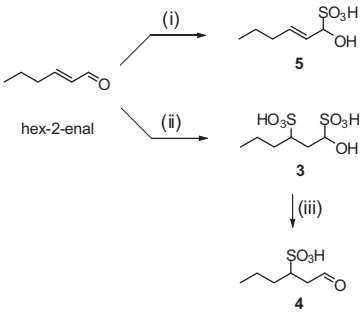

**Scheme 1.** Synthesis of sulfonic acid **1**. Reagents and conditions: (i) 40% w/v aq $NaHSO_3$ (3 equiv), $Et_3N$ (3 equiv), MeOH, rt, 24 h, 62%.




**Scheme 2.** Synthesis of alcohol sulfonic acid **2**. Reagents and conditions: (i) $Ph_3P{=}CHCO_2Et$ (1.2 equiv), $CH_2Cl_2$, rt, 47 h, 72%; (ii) 40% w/v aq $NaHSO_3$ (1.1 equiv), $Et_3N$ (1.1 equiv), MeOH, reflux, 18 h, **7**, 31%, **8**, 25%; (iii) $LiAlH_4$ (5 equiv), THF, reflux, 23 h, 80%.

It was then envisaged that oxidation of alcohol **2** would give the desired aldehyde **4**. Oxidation using either Dess–Martin periodinane (DMP) or under Swern conditions gave only trace amounts of aldehyde **4**. In both cases, separation of the water-soluble product **4** from the reaction by-products proved troublesome. These difficulties in purification prompted an alternative method to aldehyde **4** being explored. As diadduct **3** was required, it was decided to attempt to synthesise aldehyde **4** via base-induced elimination of the C-1 sulfonic acid of diadduct **3** (Scheme 3). Whilst uncommon, similar eliminations have been reported, however details are scant and conflicting.[10c,11b,18a]

Addition of bisulfite to aldehyde groups occurs rapidly, giving 1,1-hydroxysulfonic acids, which in the case of addition to α,β-unsaturated aldehydes prevents 1,4-addition. When this occurs, complex mixtures of products are often formed.[11] Therefore, in order to prepare a pure sample of the disulfonic hexenal adduct **3**, we wished to develop an improved diaddition protocol. By incorporating the addition of an amine base into the reaction, it was expected that the equilibrium between free hexenal and hydroxysulfonic acid **5** would favour hexenal, and thus the 1,4-addition of bisulfite would be greatly increased. When the reaction was undertaken in the absence of base at room temperature, after 95 h, the sole product was the hydroxysulfonic acid adduct **5** (Scheme 3). However, when 0.2 equiv of triethylamine were added, after 12 h, only the desired diadduct **3** was obtained in 88% yield.[22]




**Scheme 3.** Synthesis of sulfonic acids **3**–**5**. Reagents and conditions: (i) 40% w/v aq $NaHSO_3$ (2.1 equiv), 1:1 MeOH/$H_2O$, rt, 95 h, quant.; (ii) 40% w/v aq $NaHSO_3$ (2.1 equiv), $Et_3N$ (0.2 equiv), 1:1 MeOH/$H_2O$, rt, 12 h, 88%; (iii) $NaHCO_3$ (14 equiv), 1:1 MeOH/$H_2O$, rt, 28 h, 29% or PS-BMEP (3 equiv), $H_2O$, rt, 22 h, then 2 M HCl, 90%.