



Simple spectrophotometry method for the determination of sulfur dioxide in an alcohol-thionyl chloride reaction



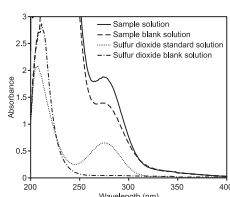
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HIGHLIGHTS

- Simple UV spectrometry method to quantitate sulfur dioxide in complex matrix.
- Excellent sensitivity, linearity and accuracy.
- Potential for real time monitoring using process analytical technology.
- Possible applications in chemical, pharmaceutical, beverage and wine industries.

GRAPHICAL ABSTRACT



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ABSTRACT

Thionyl chloride is often used to convert alcohols into more reactive alkyl chloride, which can be easily converted to many compounds that are not possible from alcohols directly. One important reaction of alkyl chloride is nucleophilic substitution, which is typically conducted under basic conditions. Sulfur dioxide, the by-product from alcohol-thionyl chloride reactions, often reacts with alkyl chloride to form a sulfonyl acid impurity, resulting in yield loss. Therefore, the alkyl chloride is typically isolated to remove the by-products including sulfur dioxide. However, in our laboratory, the alkyl chloride formed from alcohol and thionyl chloride was found to be a potential mutagenic impurity, and isolation of this compound would require extensive safety measures. As a result, a flow-through process was developed, and the sulfur dioxide was purged using a combination of vacuum degassing and nitrogen gas sweeping. An analytical method that can quickly and accurately quantitate residual levels of sulfur dioxide in the reaction mixture is desired for in-process monitoring. We report here a simple ultraviolet (UV) spectrophotometry method for this measurement.

This method takes advantage of the dramatic change in the UV absorbance of sulfur dioxide with respect to pH, which allows for accurate quantitation of sulfur dioxide in the presence of the strong UV-absorbing matrix. Each sample solution was prepared using 2 different diluents: 1) 50 mM ammonium acetate in methanol +1% v/v hydrochloric acid, pH 1.3, and 2) 50 mM ammonium acetate in methanol +1% glacial acetic acid, pH 4.0. The buffer solutions were carefully selected so that the UV absorbance of the sample matrix (excluding sulfur dioxide) at 276 nm remains constant. In the pH 1.3 buffer system, sulfur dioxide shows strong UV absorbance at 276 nm. Therefore, the UV absorbance of sample solution is the sum of sulfur dioxide and sample matrix. While in the pH 4.0 buffer system, sulfur dioxide has negligible UV absorbance at 276 nm, and the UV absorbance is attributed only to sample matrix. Quantitation of sulfur dioxide is achieved by subtracting the UV absorbance of sample solution at pH 4.0 from that at pH 1.3. The method is simple but sensitive, with a limit of quantitation of 80 $\mu\text{g L}^{-1}$. The method linearity was demonstrated from 2 mg L^{-1} to 40 mg L^{-1} with an R^2 of 0.998, and the spiked recovery ranges from 94% to 105% within the same range. The results are comparable with those

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obtained using inductively coupled plasma–atomic emission spectrometry (ICP–AES) and gas chromatography–mass spectrometry (GC–MS), suggesting that this method is accurate.

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1. Introduction

Alcohol is not reactive for nucleophilic substitution reaction because the hydroxyl leaving group is a strong base and thus not a good leaving group. One common approach to improve the reactivity of alcohol in nucleophilic substitution reactions is to convert the hydroxyl group into a better leaving group such as a sulfonate ester, phosphite ester, or alkyl halide. Thionyl chloride is commonly used for this conversion since the alkyl chloride product is very reactive, and the inorganic by-products such as sulfur dioxide and hydrogen chloride are gases, which can be purged by sparging with inert gas or degassing under vacuum [1,2].

In a process developed in Merck Research Laboratories, an alcohol is subjected to reaction with thionyl chloride to form an alkyl chloride intermediate (chlorination step), which subsequently reacts with an amide (alkylation step) to form an active pharmaceutical ingredient (API). The schematic diagram of this synthesis is shown in Fig. 1. In the original process, the alkyl chloride intermediate was isolated to remove the solvents and by-products. However, it was later determined that the alkyl chloride intermediate was a potential mutagenic impurity. Isolation and handling of this intermediate would require extensive safety measures. Therefore, a flow-through process was developed, in which the whole reaction mixture including solvents and by-products from the chlorination step was carried onto the subsequent alkylation step. One issue that arises is that sulfur dioxide reacts with the alkyl chloride intermediate under the basic alkylation conditions, resulting in yield loss and elevated level of sulfonyl acid impurity as shown in Fig. 1. As a result, sulfur dioxide has to be purged to below 5 mg/mL to achieve satisfactory yield in the next step. The degassing process was very challenging due to the high solubility of sulfur dioxide in the reaction stream, which is mainly composed of the solvent, N-methyl-2-pyrrolidone (NMP) [3]. A combination of heating, sweeping of headspace with nitrogen gas, and application of vacuum was required to reduce the sulfur dioxide to the desired level. Due to stability concerns of the alkyl chloride intermediate at elevated temperature, it is preferable to stop the degassing process as soon as the sulfur dioxide is purged to below the desired level. For this purpose, an analytical method to quickly and accurately determine the sulfur dioxide concentration during degassing was desired.

There are many reports for the analyses of sulfur dioxide, including ion chromatography (IC) [4], fluorescence [5], gas chromatography–mass spectrometry (GC–MS) [6], colorimetric [7],

ultraviolet (UV) spectrophotometry [8], and inductively coupled plasma–atomic emission spectrometry (ICP–AES). However, each method has some limitations. Very often, a large amount of organic compounds in the reaction mixture precipitate in the aqueous mobile phase that is used for IC analysis, clogging the column and contaminating the ion suppressor. In GC–MS analysis, the inlet liner is easily contaminated. Additionally, the GC column deteriorates quickly due to a strongly acidic sample matrix, requiring frequent replacement. Colorimetric method [7] typically involves lengthy sample treatment such as color development, and is not preferred for in-process control, which requires a fast analysis. The UV spectrophotometry method described by A. Syty [8] cleverly utilizes strong acid to release sulfur dioxide from an absorbing solution, and transfer it to a flow-through absorption cell using a carrier gas for the measurement of UV absorbance at 215 nm. Unfortunately, sulfur dioxide has very good solubility in NMP, the solvent that was used for the chlorination reaction even in the presence of about 1 M hydrochloric acid, the by-product of chlorination reaction. Therefore, this UV spectrophotometry method is not suitable for the samples studied in this article. A common method for fluorescence detection of sulfur dioxide is based on its reaction with o-phthalaldehyde and amine in a basic solution to form an isoindole derivative [5]. This method has good sensitivity, but often requires extensive method development for this type of highly acidic and complex sample matrix. ICP–AES is very sensitive for measuring the total sulfur in the solution, but the instrumentation can be very expensive and therefore not available in most common analytical laboratories. Fourier transform infrared is commonly used for in-process monitoring, and works well for sulfur dioxide standard [9]. However, the detection limit for a sulfur dioxide in the process under investigation here is above 20 mg mL⁻¹ due to strong matrix interferences, and thus cannot meet the requirements of this analysis.

It is well known that free sulfur dioxide in a solution has strong UV absorbance at 276 nm under acidic conditions [10]. Therefore, it is possible to use UV spectrophotometry for the determination of sulfur dioxide. However, if the sample matrix also shows strong UV absorbance at 276 nm, accurate quantitation of the sulfur dioxide will be extremely difficult.

In this study, we report a simple but sensitive method for the quantitation of sulfur dioxide by taking advantage of the dramatic change in UV absorbance of sulfur dioxide with respect to pH. This method has been demonstrated to be sensitive and accurate for the quantitation of sulfur dioxide with minimal sample treatment even in the presence of strong background absorbance from reaction mixture. This method can be applied to quantitate sulfur dioxide in most thionyl chloride reaction streams.

2. Experimental

2.1. Apparatus and reagents

All absorption spectral recordings and absorbance measurements were performed on a Cary-300 UV spectrophotometer (Varian, USA) with 1 cm light-path quartz cuvette. The cuvette was

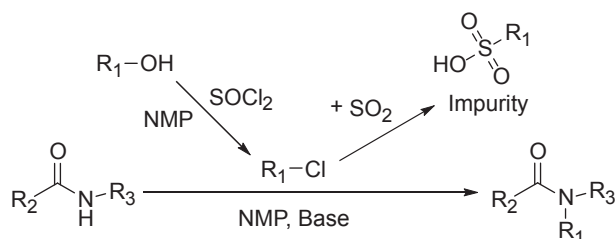


Fig. 1. Reaction scheme of chlorination and alkylation.

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