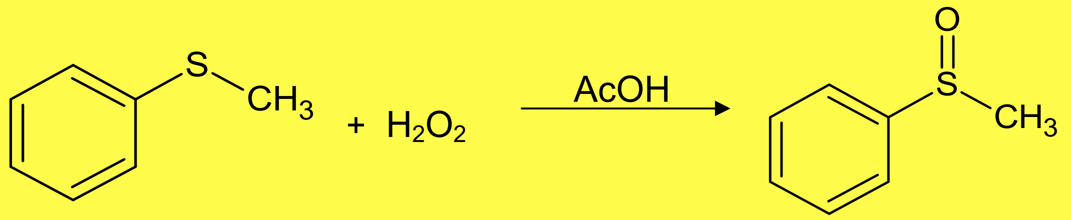
Application Note 45: The safe and controlled oxidation of thioanisole with 50 wt. % hydrogen peroxide

Abstract

This application note demonstrates the oxidation of thioanisole using hydrogen peroxide in continuous flow. It highlights the use of 50 wt% hydrogen peroxide which can be pumped neat with Vapourtec systems. Both cooled and heated conditions were explored for this exothermic reaction. The reaction temperature was controlled using a Vapourtec cooling module for the sub-ambient conditions. To explore the highest possible throughput, mildly heated conditions were also explored.



Scheme 1

Background

The key features of this application note include:

- Safe handling and controlled reaction with 50 wt.% aqueous hydrogen peroxide.
- Highly selective oxidation of sulphoxide formation from thio ether.
- Optimal output of 225 g/h with a single reactor (37.8 kg/week).
- Demonstration of the safety features incorporated into Vapourtec systems.

Hydrogen peroxide is a strong oxidizer which finds many uses in the chemical industry. However, due to this reactivity, care is needed when utilizing it in reactions to limit the impact of an exothermic reaction. As a result, in batch, hydrogen peroxide is added slowly/dropwise to the reaction mixture to avoid a rapid reaction, excessive heating or reaction run-away. Flow chemistry is a much safer approach to undertaking these exothermic reactions, the key reasons being:

- Only a small inventory of reactive materials is present in the reactor at any time.
- The surface area to volume ratio of flow reactors is much larger than their batch counterparts and therefore are much more capable of removing heat from a reaction.
- The reagents are continually pumped ensuring the reaction progresses at a controlled rate.
- Should the temperature of the flow reactor start to rise this can be readily observed and corrective actions taken to slow or even stop the reaction.

50 wt% hydrogen peroxide was used in this application note, which can prove corrosive to many substances and chemical apparatus. With the Vapourtec systems, there are no issues or side reactions with the tubes or pumps. The Vapourtec systems are versatile and resilient.

Method

Setup

The flow reactor was set up using the Vapourtec E-series as shown in figure 1.

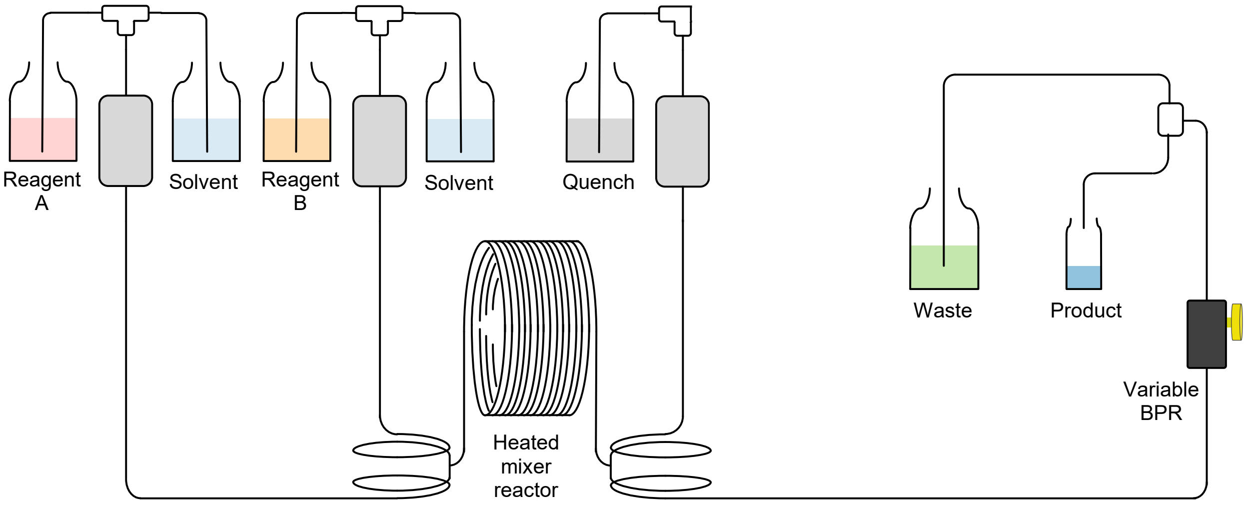


Figure 1

A heated mixer reactor was used and the reactor volume was varied between 2 and 10 mL as required to achieve the desired reaction residence time. Pressure was controlled by a variable back pressure regulator (BPR). The elution outflow was collected via the waste/collection switching valve. The Vapourtec systems have important safeguards that ensure exothermic reactions can be run safely:

- <u>Over-temperature shutdown:</u> If the temperature of the reactor exceeds the set temperature by more than 8°C then the pumps are automatically shut down and the reactor cooled.
- <u>Over Pressure conditions:</u> It should be noted that flow reactors have no head space therefore there is no stored energy by virtue of a pressurised gas volume. Should the reactor become over pressurised for any reason there are two safety features: i) The back pressure will open acting as a pressure relief valve to release the pressure, ii) There is an overpressure trip that when activated will automatically stop the pumps and cool the reactor.

Pump Tubing

The E-Series is fitted with three high performance V-3 peristaltic pumps and features a fluoropolymer tube as its core. The pumps feature more than one different tube type to ensure the largest range in compatibility of solvents. Therefore the correct selection of tubing is crucial for any given reaction.

A table showing recommended tube type compatibility with a wide selection of solvents, acids and bases is available within the E-Series manual and also built into the user interface software.
It is important to note, each V-3 pump can achieve a maximum of 10 mL/min.
The red tube was used for the hydrogen peroxide and the blue tube was used for the acetic acid and acetonitrile.

Reagents

All reagents and solvents used were purchased from Sigma-Aldrich.

Reagent A – aqueous hydrogen peroxide (50 wt.%)

Reagent B – 1 – 4M thioanisole in acetic acid

Reagent C – Acetonitrile

System Parameters

System solvent A:	Water
System solvent B:	Acetic acid
System solvent C:	Acetonitrile
Solution A:	Hydrogen peroxide 50 wt%
Solution B:	Thioanisole in acetic acid
Solution C:	Acetonitrile (pump channel C was used to dilute and thereby quench the reaction)
Flow rate:	Variable
Reactor volume:	2 – 10 mL reactor
Reactor temperature:	-10 – 60^{o}C
System pressure:	2 bar

The reaction process followed the sequence of steps listed below:

1. Prepping the system
   The system was primed by running the system solvent through the pump and reactor, ensuring all connections are correct.

2. Product pumping and collection
   Each reaction was run automatically using the FlowWizard software on the E-Series. After prepping the system, the parameters were set for the reaction and allowed to run until completed. FlowWizard accurately collects the desired amount of product from the steady state using the automatic collection gantry valve. The collection vial was filled with acetonitrile to dilute and quench the products.

3. Analysis
   A small amount of the resulting crude product was analysed by HPLC to determine the conversion using an H_2O/acetonitrile gradient. For purification, the crude product is neutralized with sodium hydroxide and extracted with dichloromethane. [Safety-Ensure there is no remaining hydrogen peroxide before evaporation].

Results and Discussion

Reaction conditions

The flow system as set up used acetonitrile as a third reagent to dilute and slow the reaction prior to quenching. This oxidation does not need heat, light or a catalyst to react, just the presence of hydrogen peroxide, thioanisole and acetic acid. The acetonitrile (third reagent) was in large excess to prevent further reaction before the products were collected.

The following table shows the different reaction conditions used. The hydrogen peroxide concentration was 50 wt% and always in a 4 fold excess to thioanisole, volumes and concentrations were calculated accordingly.

Run No.	Conc. of starting material (M) and ratio to AcOH	Flow rate of SM (ml/min)	Flow rate of H_2O_2 (ml/min)	Temp. (°C)	Reactor size (ml)	Reaction time (min)	Conversion (%)	Output (g/h)
1	8.51 (neat)	1.70	3.30	40	10	2	9.01	11.0
2	6.8 (2:1)	1.96	3.04	40	10	2	22.59	25.4
3	5.7 (1:1)	2.18	2.82	40	10	2	65.73	68.8
4	4.9 (1:1.5)	2.37	2.63	40	10	2	85.56	83.5
5	4 (1:2)	2.62	2.38	40	10	2	100	88.2
6	4 (1:2)	2.62	2.38	10	10	2	20.38	18.0
7	4 (1:2)	2.62	2.38	30	10	2	95.26	84.0
8	4 (1:2)	2.62	2.38	40	10	2	100	88.2
9	4 (1:2)	1.05	0.95	60	2	1	100	35.3
10	4 (1:2)	1.40	1.27	60	2	0.75	100	47.1
11	4 (1:2)	2.10	1.90	60	2	0.5	85.58	60.5
12	4 (1:2)	5.24	4.76	60	10	1	100	176.3
13	4 (1:2)	6.71	6.09	60	10	0.78	100	225.8
14	2 (1:4)	3.93	3.57	60	5	0.75	100	66.0

Table 1

Effect of acetic acid

Run numbers 1-5 change the ratios of starting material to acetic acid, including neat thioanisole with no acetic acid. All other reaction parameters were kept the same, including a 4 fold excess of hydrogen peroxide.

The results show that acetic acid is important to the reaction. This is likely to be due to two different reasons. First is simply the solubility, thioanisole is soluble in acetic acid and only sparingly soluble in water. Therefore increasing the amount of acetic acid would increase the solubility and reduce the tendance to form a biphasic mixture on contact with the 50% H_2O_2 in the reactor. Secondly, the interaction between acetic acid and hydrogen peroxide aiding the oxidation is another cause for the improved conversion.

Effect of temperature and potential oxidations

Oxidation with hydrogen peroxide is an exothermic process and traditional reactions in batch cool the reactions using an ice bath to prevent excessive heat generation and run-away reactions. Thioethers, such as thioanisole, can be oxidised into more than one product. In this case the thioether oxidises to a sulphoxide, then a sulphone. In this application note the sulphoxide is the desired product and the sulfone is an unwanted over oxidised side product.

As stated before, the advantages of flow chemistry allow the reaction temperature and temperature gradient to be controlled. Therefore it would be ideal to accurately test the effects of temperature on output and to control and prevent any possible over oxidation. Increasing the temperature would intensify the process, whilst decreasing the temperature may reduce any over oxidation. Demonstrating a cooled reaction could have many applications for similar reactions which are also temperature sensitive.

Run numbers 6-9 clearly show that increasing the temperature increases the rate of reaction. In the case of this reaction, quenching the reaction right after the reactor produces no observable side reactions or over oxidation. Therefore in this experiment’s case, to improve throughput, it is better to use a higher temperature.

For other potential reactions which may be temperature sensitive or generate excessive heat will need a lowered temperature to be controlled. At 10°C, an output of 15.9g/h was obtained for a single 10ml reactor. By decreasing the concentration of the starting material, increasing the acetic acid ratio and increasing the reaction time, the reaction does achieve 100% conversion, albeit at a slightly lower output.

Figure 2 shows HPLC spectra for run number 3 containing the starting material, product and solvents when the reaction has not gone to full conversion. These peaks were the only ones observed on all spectra, including 60°C tests, indicating that there is no over oxidation or other side reactions occurring during the flow process.

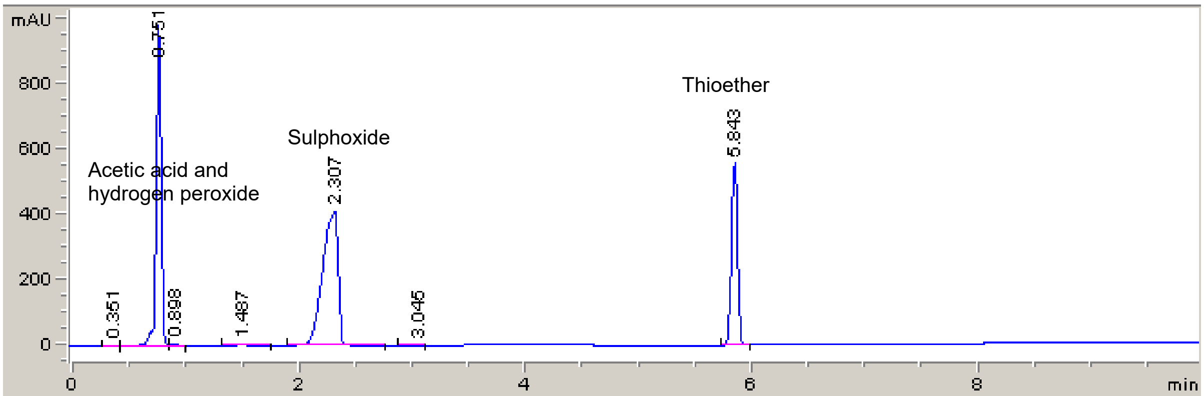


Figure 2

Figure 3 shows HPLC spectra for run number 13. No starting material or over oxidised sulphone are present, proving that the reaction is clean and can selectively oxidise to only the sulphoxide even at elevated temperatures and high throughput.

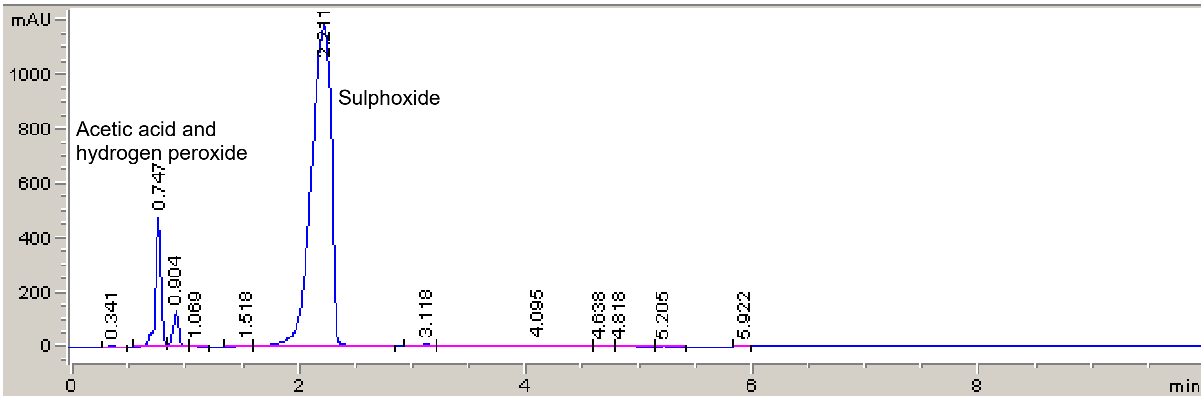


Figure 3

To investigate the possibilities of over oxidation, a sample batch reaction was set up and analysed. Figure 4 shows the products from the batch reaction after 2 hours. Sulphone was present even though the thioether starting material was not completely consumed. A small amount of the sulphone was observed even after a few minutes of reaction.

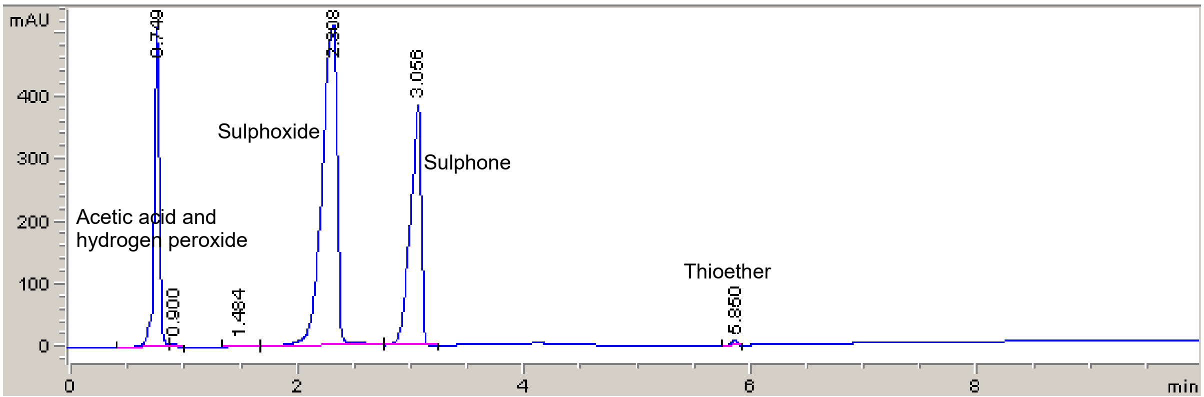
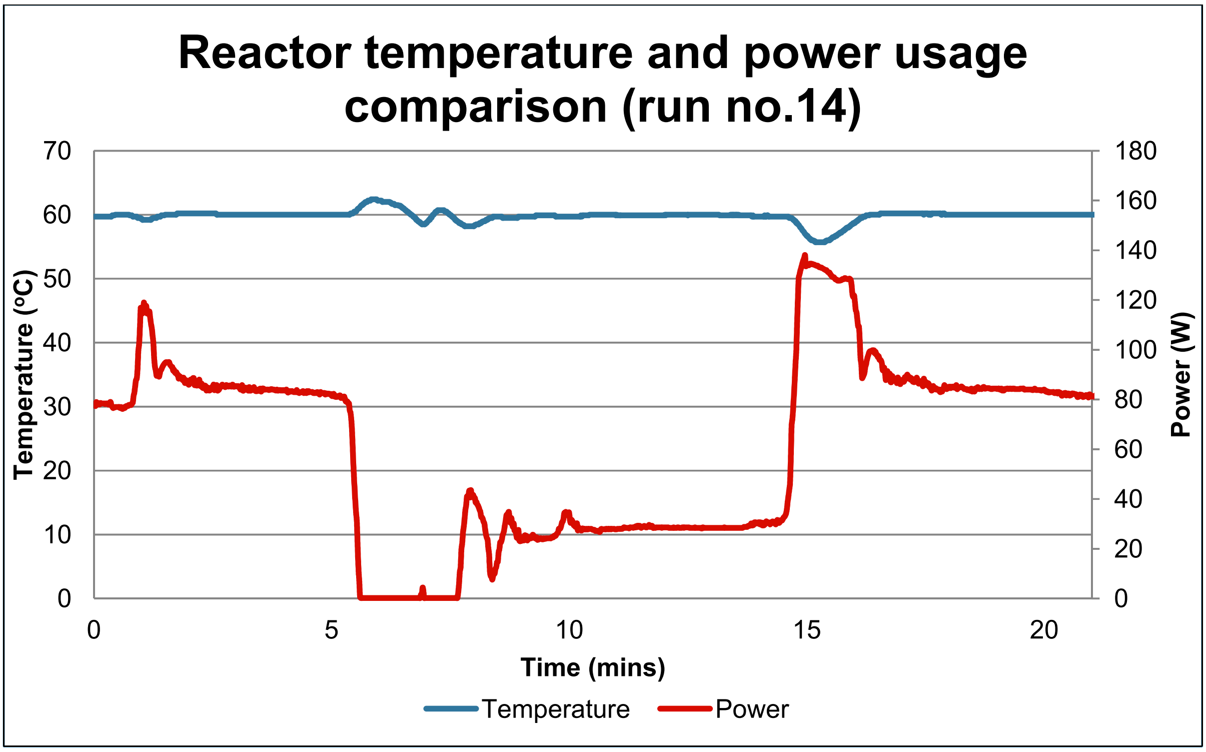


Figure 4

This shows that the reaction for this application note is prone to over oxidation. However with flow, controlling the temperature, the slow continuous addition of products and immediate quench after the reactor, circumvents these problems and the sulphone is not present.

To demonstrate the potential heat generation and the importance of controlling the temperature, the temperature and power input to the reactor were compared. The Vapourtec R-Series system and Flow Commander were used to log this data. The data obtained is shown in graph 1 below.



Graph 1

The reactor was heated while pumping solvents only and allowed to reach a stable temperature of 60°C, which gave a stable input power of 80 watts. Once the reactor was stable a slug of reagent was pumped through the reactor. Referring to the graph above, after 5 minutes the reactants started to mix within the reactor. The control system detected the slight temperature rise and adjusted the reactor's input power to maintain the reactor temperature at 60°C. After a short period the reactor temperature stabilised and returned to 60° and the reactor power once again stabilised but this time at a value of 30 watts. Once the slug of reactants exited the reactor (15 minutes) the power was observed to once again return to 80 Watts. The difference between 80 watts (solvent only) and 30 watts (with reactants) allows the quantification of the reaction heat output. In this case 50 Joules/second or 50 watts.

The reaction conditions for graph 1 are listed in table 1, run number 14. The concentration was halved to 2M and the reactants were added slower in the experiment to prevent a large spike in temperature. At 4M, the temperature increase when mixing the reactants exceeded +8°C, which was the temperature trip for the system for safety reasons.

Decreasing reaction time and optimisation

Run numbers 9-11 investigate the lowest reaction time needed for higher temperatures. The reactor volume was decreased to 2ml as flow rates would exceed pump capacities with a 10ml reactor. At 60°C, a reaction time as low as 45 seconds results in 100% conversion. Applying this with larger capacity pumps and a larger reactor, such as a 10ml reactor could lead to reaction outputs of over 225g/h.

Scale up

Run numbers 12-13 scale up previous results to achieve a high output. Applying the temperature and residence times from optimisation, run number 13 successfully achieved an output of 225g/h with 100% conversion with a single 10ml reactor, as shown in figure 5.

These reactions experience a temperature increase significantly above the reactor temperature. To enable this the over-temperature trip setting was increased for this run. The reaction temperature was monitored carefully throughout this run.

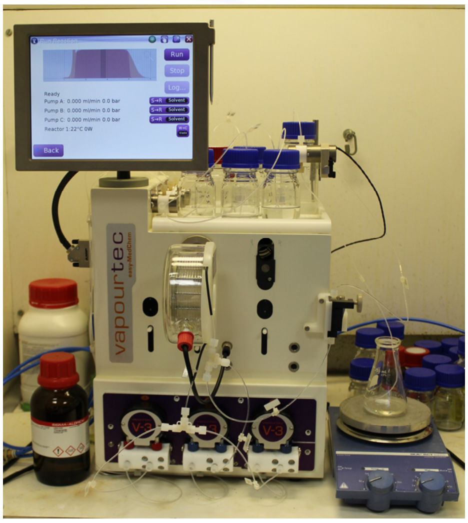


Figure 5

Conclusion

This application note set out to investigate the pumping capabilities of hydrogen peroxide in flow and to apply it to an example reaction. There were no complications running 50 wt% hydrogen peroxide or neat acetic acid throughout the experiment. Further, the ability to run the oxidation under lower temperatures was investigated and demonstrated the capability to keep a consistent cooled temperature. The output of this selective reaction was also explored, an output of 225g/h was achieved with a single 10ml reactor without over oxidation.