Cryogenic Applications in Flow Chemistry Enabled by the IceCube™ Flow Reactor

1st application: Swern Oxidation

INTRODUCTION

Exothermic reactions, by their very nature, often progress rapidly through unstable intermediates. Maintaining a firm control over parameters such as temperature and pressure is problematic, so their utilization is limited in synthetic practice. However, flow techniques have the potential of keeping such reactions under control via their improved heat and mass transfer capabilities, allowing one to exploit untapped or avoided chemistries.

Swern oxidation is well known for the oxidation of alcohols to their corresponding carbonyls and it demonstrates good functional group selectivity. However, their regular application has been limited so far due to their low reaction temperature requirement, which is inevitable for maintaining a stable reactive intermediate. In batch, the 'activated' dimethyl sulphoxide (DMSO) decomposition has been reported to occur above -60°C.

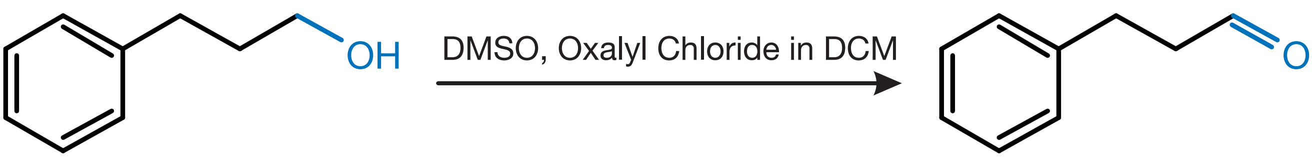
In this application note we are about to demonstrate a classical Swern oxidation, conducted in ThalesNano's novel IceCube™ Flow Reactor, as an example of performing high energy reactions safely and selectively (Scheme 1).

INSTRUMENTATION

The IceCube™ is a low temperature, continuous flow reactor. The reagents are continuously pumped through the reaction zone and the product is collected in a flask after the reaction takes place. The device has two reaction zones, which can each be cooled down or heated to -70°C – +80°C and -30°C – +80°C respectively, so multi-step reactions may be performed. This includes reactions where hazardous intermediates can be formed and reacted without isolation. The IceCube™ has also been utilized for performing other hazardous reactions including ozonolysis, diazotization, lithiation, and nitration.

EXPERIMENTAL PROCEDURE

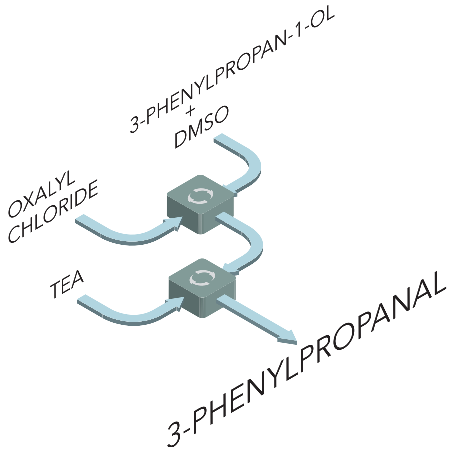
In the classical Swern oxidation both the DMSO and the electrophilic activating agent are in an inert medium. At temperatures <-50°C their reaction results in the formation of the 'activated' dimethyl sulfoxide. If oxalyl chloride is used as the activating agent the reaction also leads to a rapid CO and CO_2 evolution. We ensured the highest possible alkoxysulfonium chloride intermediate formation, not only by adding the alcohol to the DMSO initially, but by keeping a steady cryogenic environment within the IceCube™ Flow Reactor as well.



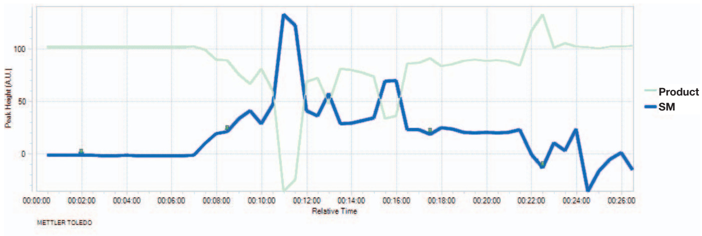
Scheme 1. Swern oxidation of 3-phenylpropan-1-ol to 3-phenylpropanal

By doing so we successfully avoided the chloromethyl methyl sulfide formation and, therefore, the thioacetal formation up to -10°C. The prepared intermediate was then subsequently easily converted to the desired aldehyde by introducing triethylamine (TEA) solution into the flow stream.

For the oxalyl chloride solution we dissolved 1 mL oxalyl chloride in 25 mL dichloromethane (DCM). In a separate container we added 1 mL of 3-phenylpropan-1-ol and 1.7 mL DMSO to 15 mL DCM. TEA solution was prepared by adding 7 mL TEA to 7 mL MeOH. The above solutions were fed into the IceCube™ Flow Reactor as demonstrated in Scheme 2. The flow rate of the oxalyl chloride solution was 0.96 mL/min. The flow rate of the combined solution (alcohol and the DMSO) was 1.9 mL/min. The flow rate of the TEA was 0.76 mL/min. The optimization process was followed by in-line analysis using a FlowIR™ system. The product was continuously introduced into the FlowIR™, which was set to the two specific wavenumber ranges of the starting material (1025 cm^{-1}) and the product (1210-1194 cm^{-1}). The system monitored these over time. The spectra on Scheme 3. shows the in-line monitoring of the reaction carried out at -30°C, which indicates an average 80% conversion. The collected product was extracted first with water, then DCM before finally with brine NaCl. The solution was then dried on Na_2SO_4. After filtration GC-MS analysis was performed, which results are presented in Table 1.



Scheme 2. Experimental setup of converting 3-phenylpropan-1-ol to 3-phenylpropanal, utilizing Swern oxidation in the IceCube™ Flow Reactor.



Scheme 3. In-line reaction during the Swern oxidation of 3-phenylpropan-1-ol.

Entry	Temperature	Conversion [%]	Selectivity [%]
1	-30	100	100
2	-20	100	100
3	-10	100	100
4	0	100	60

Table 1. The effect of temperature on selectivity and conversion during the Swern oxidation of 3-phenylpropan-1-ol.

RESULTS

Swern oxidation was successfully performed resulting in quantitave conversion and selectivity (confirmed by GC-MS). As the result of the temperature screening we found that a rise in temperature did not trigger byproduct formation up to -10°C in the IceCube™ Flow Reactor, whereas in batch, byproduct formation was reported above -60°C. Above this temperature the same byproduct (thioacetal) was formed as in batch.

CONCLUSION

We were able to perform a Swern oxidation reaction in a continuous flow system resulting in quantitative conversion and selectivity. The use of the continuous system allowed us to perform the reaction at a higher temperature without side product formation. The applied technology not only saves time, but also allows for an easier scale-up possibility.

LEGAL

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