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Continuous Ozonolysis as a Key Step of the Darunavir Synthesis Using the IceCube™ Flow Reactor

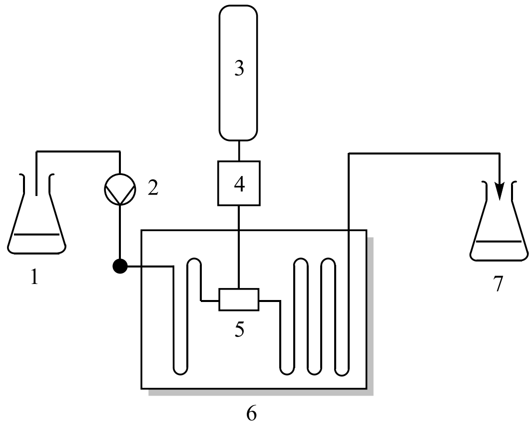


Figure 1. Instrument part description
1. Starting material solution 2. Pump 3. O_2 tank 4. Ozone Module 5. Mixer 6. Reactor Module 7. Quenching solution

Introduction

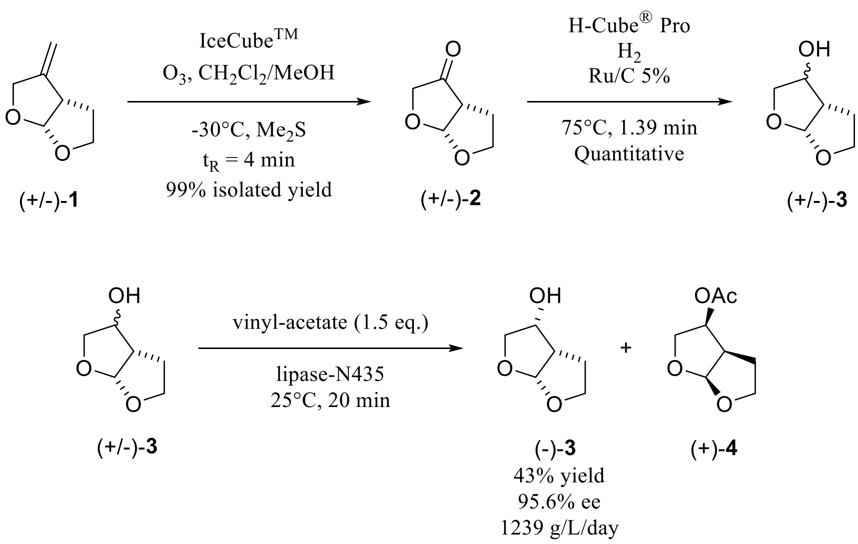
AIDS is one of the most threatening diseases spread across the planet, affecting about 35 million people worldwide.[1] To improve the quality of life of those affected by HIV, a number of antivirals were developed, such as Darunavir. This molecule has a complex bicyclic core, the synthesis of which is well documented in the literature.[2–5]

State of the art: An approach described by Ghosh and his co-workers includes an ozonolysis step, which is performed under batch conditions resulting in the desired ketone with 98% yield after 3 hours.[6,7] However, handling the gaseous ozone and working at a very low temperature (78°C) is inconvenient. Adapting the synthesis to a continuous flow system provides a safe and rapid alternative solution by using *insitu* generated ozone, a closed system, and higher temperatures.[8]

In this application note, we demonstrate that continuous flow ozonolysis can easily be carried out utilizing the IceCube™ Flow Reactor, developed by ThalesNano, in a safe and efficient way.[9]

Instrumentation

The ThalesNano IceCube™ is a revolutionary low temperature continuous flow reactor designed for performing highly exothermic reactions such as ozonolysis, diazotization, lithiation, and nitration. It consists of four different modules (Figure 1). The solution of starting materials is pumped into the tempered reaction module, where it is mixed with the ozone, generated from the Ozone Module™. The Ozone Module™ enables *in situ* generation of ozone from oxygen, while the ratio of the two components is precisely controlled. For quenching, there are two options: A) a quenching stream can be introduced to the system between the reaction module and the quenching module (not applied by the authors) B) to pump the reaction mixture directly into the quenching solution, as it can be seen in Figure 1.



Scheme 1.

The ozonolysis reaction was performed in the ThalesNano IceCube™ Flow Reactor (Figure 1). The reactor module can be tempered in a broad range (-70°C-+80°C and -30°C-+80°C for the two zones), thus, the execution of cooled and heated reactions is also possible. The ozone is produced from oxygen gas (2.5 purity, industrial grade, 5-6 bar, Linde) in the Ozone Module™, which is also available as a part of the IceCube™ system. The module is capable of forming ozone in 10-14% of oxygen introduced. The gas flow rate can be changed between 1 and 100 mL/min, the system can hold pressure up to 6 bar. The pumps for the ozonolysis are rotary piston pumps built in the device. The liquid flow rates are variable from 0.1 to 4 mL/min.

Risk assessment and hazards: The most critical step of the procedure is the quenching of the reaction mixture. It is necessary to use at least 3 equivalents of quenching reagent, and one must always ensure that the solution is free of peroxides before work-up. Under no circumstances should the user start working up the solution, if the peroxide test is positive.

Experimental

The synthesis of (3aR,6aR)-tetrahydrofuro[2,3-b] furan-3(2H)-one (+/-)-2

SYNTHESIS IN BATCH

A stream of ozone was dispersed into a solution of alkene **(+/-)-1** (1 g, 7.94 mmol) in methanol and CH_2Cl_2 (1:1, 52 mL) at -78°C. After 3 h, TLC (20% EtOAc in hexane) indicated the reaction had gone to completion. The reaction was quenched with dimethyl sulfide (3.5 mL, 47.66 mmol) and the resulting mixture was allowed to warm to room temperature, concentrated under reduced pressure, and dried under vacuum to yield the product **(+/-)-2** as a strong yellow oil in 98% yield (0.99 g).

SYNTHESIS USING ICECUBE™

A solution of alkene **(+/-)-1** (0.012 g, 0.09 mmol) in dichloromethane and methanol (1:1, 20 mL) was flowed through the IceCube™ Flow Reactor at -30°C (4 min residence time; flow rate 1.0 mL/min). The reaction mixture was quenched with dimethyl sulfide (3.5 mL, 47.66 mmol) dissolved in DCM:MeOH (1:1, 100 mL). The ozone module metered 50 mL/min at approximately 10-12% O_3. The progression of the reaction was checked by TLC (16% EtOAc in hexane, SM Rf: 0.57, Product Rf: 0.41, colouring agent: phosphomolybdic acid), and GC-MS. The collected mixture was concentrated to 15 mL under reduced pressure and extracted with water. The organic phase was collected and dried over magnesium sulfate and evaporated to dryness to yield product **(+/-)-2** as pale-yellow oil with >99% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26-2.2.20 (m, 3H), 3.00 (dd, J = 11.7, 5.2 Hz, 1H), 3.80 (dd, J = 17.0, 9.0 Hz, 1H), 4.09 – 4.02 (m, 1H), 4.15 (s, 2H), 6.07 (d, J = 5.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 215.48, 107.89, 71.70, 67.67, 49.58, 30.39.

Results and discussion

The ketone **(+/-)-2** was synthetized using IceCube™ Flow Reactor in 99% isolated yield, which meets the results accomplished by the conventional batch methods (98%). With the IceCube™ it has been shown that by reducing the reaction time from 3 hours to 4 minutes, the space-time yield achieved in flow (2281 g/L/day) massively exceeds the value obtained with the original batch ozonolysis (152 g/L/day). The optimal reaction parameters are shown in Scheme 1. The structural confirmation of the product was achieved by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. In a following step the obtained ketone (+/-)-2 was reduced by catalytic hydrogenation in H-Cube® Pro continuous hydrogenating system. The desired enantiomer was isolated by enzymatic kinetic resolution (see Scheme 1).

Conclusion

The IceCube™ Flow Reactor was demonstrated as an excellent platform to perform ozonolysis en route to Darunavir. The described procedure resulted in a significantly higher space-time yield, while also avoiding the hazards of operating ozone in a batch setting. In conclusion, the IceCube™ Flow Reactor is the perfect solution to carry out ozonolysis in a safe and efficient manner.

Acknowledgement

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