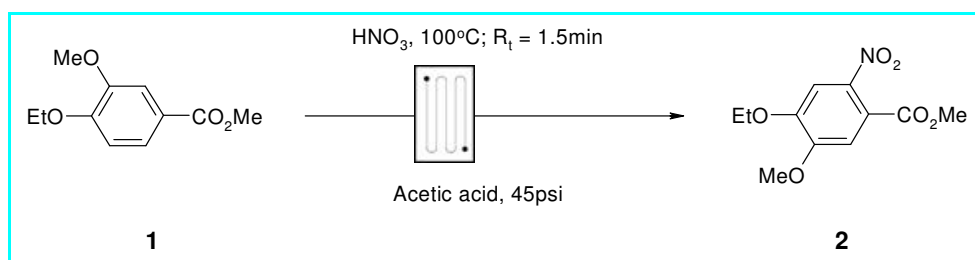


FlowSyn™ Application Note 22: Flow Nitration



Introduction:

Nitration is an important synthetic procedure that, following reduction of the nitro group, provides a useful route for the introduction of amino groups onto aromatic rings.

Although there are a number of methods for effecting nitration, the in situ generation of the requisite nitronium ion from the acid catalysed dissociation of nitric acid is perhaps the most ubiquitous. Since this is often the rate determining step, the rate and selectivity of nitration can usually be well controlled by the choice of acid and reaction conditions to cleanly afford the desired product.

The combination of acetic and nitric acids is a relatively mild method, but is well suited to continuous flow implementation in that by operating at elevated temperature, short reaction times and high selectivity can be achieved whilst minimising the amount of corrosive (and potentially explosive) hot nitrating mixture present in the reactor at any one time.

- In this Application Note a static mixer chip is used to control both temperature and mixing. Under these conditions, selective mono-nitration can be rapidly performed at elevated temperature to maximise throughput.
- The substrate is a chemotype often used in the synthesis of endothelial growth factor inhibitors.
- A short initial study was performed using the 'Multiple Experiment Package' to profile the nitration and revealed that whereas the reaction takes several hours at room temperature, it is complete in 1.5 min at 100°C.
- The nitrated product is conveniently isolated by direct precipitation from water.
- Throughput can be increased by attached a PTFE coil as an extended residence unit to the outflow of the mixer chip.

Method:

System solvent: Acetic acid.

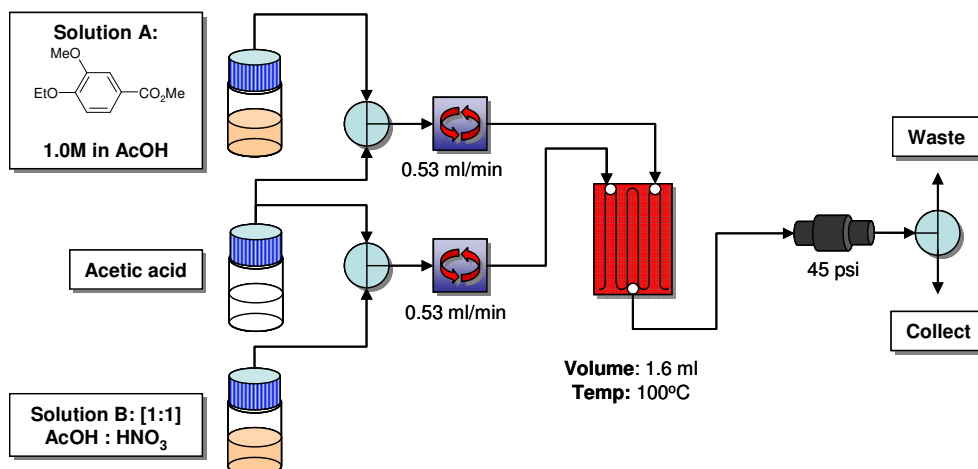
Stock solution A: Methyl 3-methoxy, 4-ethoxybenzoate (4.00g, 19.0mmol) diluted to 25ml in acetic acid.

Stock solution B: Nitric acid (66-70%): acetic acid [1:1].

The FlowSyn was fitted with a 2.0ml static mixer chip and a 45psi fixed back pressure regulator.

The reactor outflow was directed into a 1000ml collection bottle contained water (400ml) that was continually stirred using a magnetic stirrer.

Schematic:



| System Configuration | | | |
|----------------------|------------|--------------------|------------|
| RH reactor: | | LH reactor: | |
| Type: | Coil | Type: | None |
| Material: | HT PTFE | Material: | |
| Volume: | 1.60 ml | Volume: | |
| Max Temp: | 260°C | Max Temp: | |
| System Dead Volume: | 0.00 ml | Heat Exchanger: | Yes |
| Minimum Pressure: | 0 psi | Pump Start Delay: | 30 s |
| Maximum Pressure: | 200 psi | Pressure Units: | psi |
| Pressure Threshold: | Off | | |
| Wash Flow Rate: | 5.0 ml/min | Equil. Flow Rate: | 0.5 ml/min |

| Auto Set Up | | | |
|--------------|--------|------------------------|-------------|
| Inlet A: | Bottle | Coil Residence Time: | 00:01:30 |
| Inlet B: | Bottle | Column Residence Time: | 00:00:00 |
| Volume A: | 20 ml | Total Flow Rate: | 1.06 ml/min |
| Volume B: | 20 ml | Pre Collect: | -2.00 ml |
| A:B Ratio: | [1:1] | Post Collect: | -2.00 ml |
| Coil Temp: | 20C | Final Wash: | 4.00 ml |
| Column Temp: | 100C | Intermediate Wash: | 0.00 ml |

Throughput = 6.1g/h (1.6ml reactor)

(NB: By attaching a 14.0ml HT PTFE coil reactor to the outflow from the mixer chip and increasing the flow rate proportionally to maintain the same residence time (FR = 10.3ml/min; Rt = 1.5min), the throughput can be increased to 60g/h.)

When the reaction was complete the product was collected by filtration of the aqueous suspension. The solid was washed on the filter with water (2 x 30ml), then 30/40 petroleum ether (1 x 30ml), before being dried under vacuum o/n to afford **2** as a pale yellow powder (4.25g, 85%).

HPLC: $R_t = 2.79\text{min}$ ($R_t(\text{s/m}) = 2.67\text{min}$): 100% purity @ 254nm.

$^1\text{H-NMR}$ (CDCl_3 ; 400Hz): 1.45 (3H, t, $J=7$), 3.82 (3H, s), 3.90 (3H, s), 4.10(2H, q, $J=7$), 7.00 (1H, s), 7.35 (1H, s).

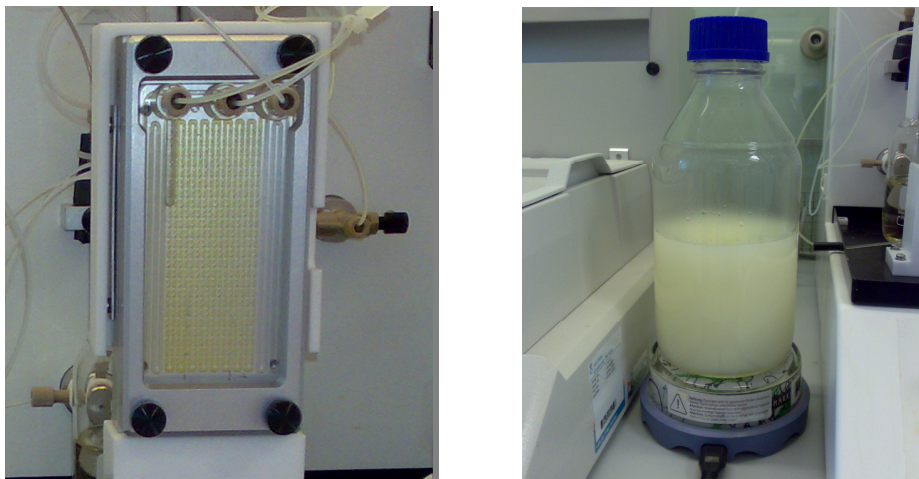


Figure 1. Nitration underway in a mixer chip and collecting the reaction product by direct precipitation from water.