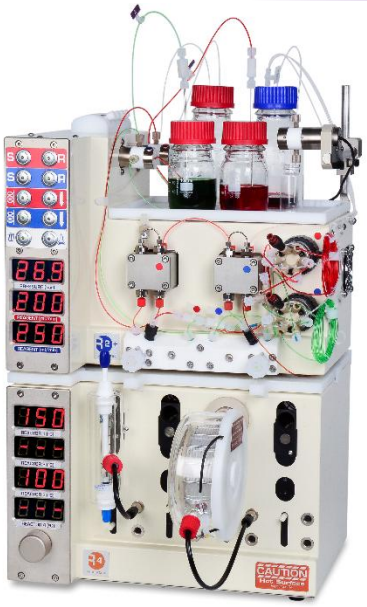


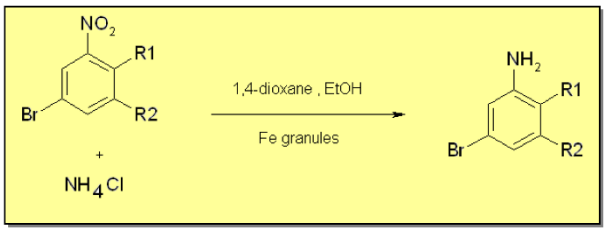
Application Note 17:

Simplified Aromatic Nitro Reduction in the Presence of an Aryl Halide

Produced by Vapourtec

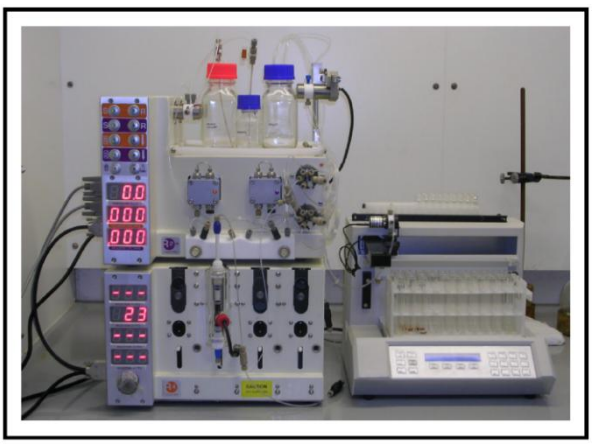
Abstract

This study demonstrates a flow based approach to reduction of an aromatic nitro compounds using a column of iron granules as the catalyst.



For more details, please contact:
Vapourtec Application Support
application.support@vapourtec.com or call:
+44 (0) 1284 728659

Setup:



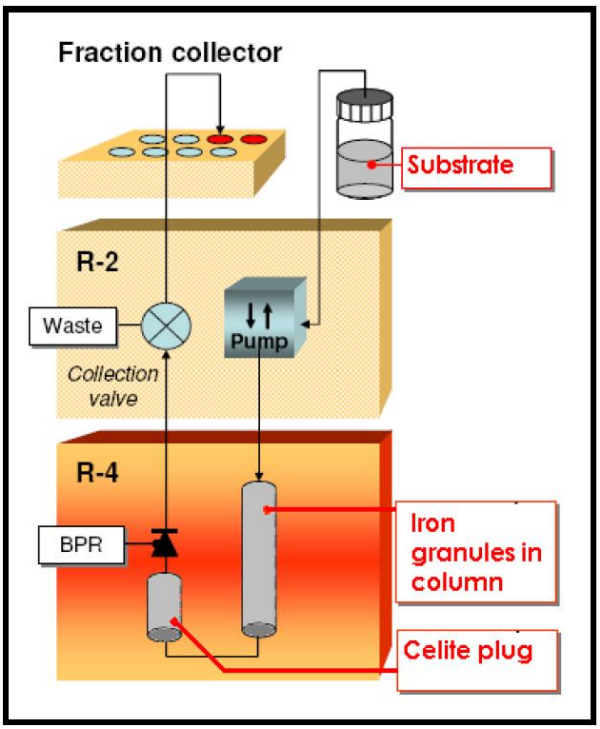


Figure 1. Representative flow reactor setup for Aromatic Nitro Reduction

Background:

Reduction of aromatic nitro compounds with iron is a facile way to convert an aromatic nitro group to the corresponding amino group in the presence of an aryl halide. 15-20 g of the above compound

was required for an array template, and although refluxing the nitro compound in water:ethanol (3:1, v/v) in the presence of iron and ammonium chloride gave good conversion to desired product, removal of the iron oxide and ammonium salts proved to be difficult, and yields were 70% at best.

As a result, a continuous flow process was developed by packing iron granules into an Omnifit column in order to produce 16 g of the desired compound (4x4 g batches), in excellent yield and purity and with minimum work-up.

Issues:

Column Blocking

Formation of iron oxide can cause the column to block up. It was postulated that dispersing the iron with an inert filler (such as celite or mol sieves) might help to alleviate this problem, but after limited attempts no significant benefits to this approach were demonstrated.

It was observed that the column lifetime could be extended by the use of iron granules instead of iron powder, as this prevents the formation of plugs of iron oxide.

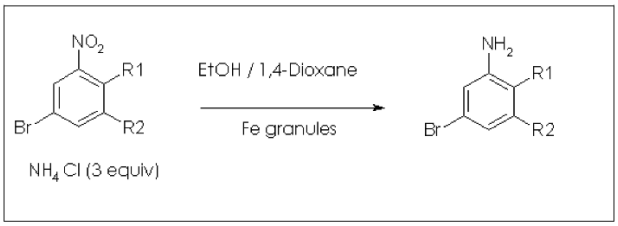
Leaching from the column

Iron oxide leaches out of the column and frequently caused blockages in the tubing at the outlet. It was found that introducing a short plug of celite inside the column (after the iron) successfully negated this issue.

Solubility

This particular compound had low solubility in most organic solvents, hence the very precise volumetric ratios in the experimental. Acetic acid could not be used in this case as the solvent/proton source (due to an acid-labile group at R1), although it has been used successfully for other substrates (on a much smaller scale).

Method:



The nitro compound (4.7 g, 14.41 mmol) was dissolved in ethanol (275 ml)/1,4-dioxane (250 ml). To this was added a solution of ammonium chloride (43.2 mmol) in water (60 ml).

An Omnifit column (15 mmx100 mm) was packed with iron granules (Alfa Aesar, 39708, size 1-2 mm) followed by a short plug of celite. The above solution was pumped at 2.0 mL/min through this column then through a 40 psi back pressure regulator.

The column was heated to 100 °C.

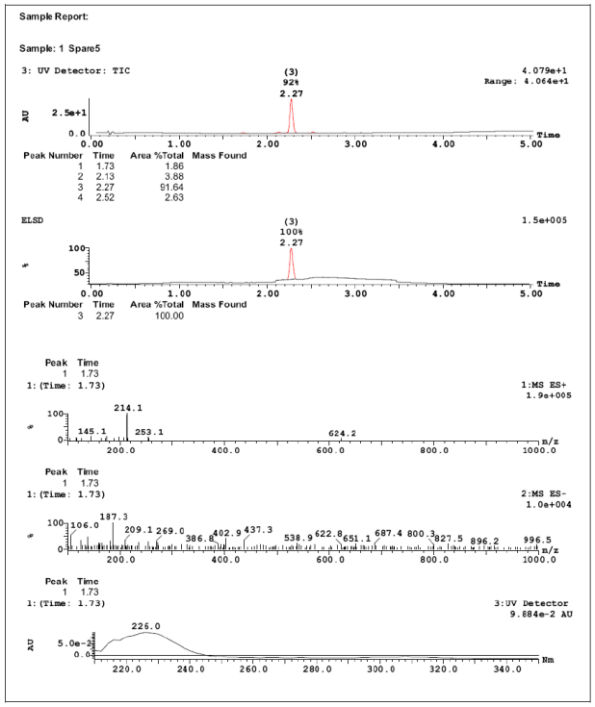
The collected solution was concentrated before partitioning between water/EtOAc. The organic phase was evaporated to dryness to give the title compound as a brown foam (3.84g, 90%).

Extensive optimization of the flow conditions and temperature was not performed.

A flow of 2.0 mL/min was found to give a good balance between throughput/system pressure.

Results:

The LCMS trace for the product is shown below.



Conclusion:

This short study demonstrates a simple but effective flow approach using an immobilized metal catalyst to provide multi gram quantities of the target compound with minimal workup.

Acknowledgements:

This application note was contributed by

Rob Wheeler
GlaxoSmithKline
Gunnels Wood Road
Stevenage