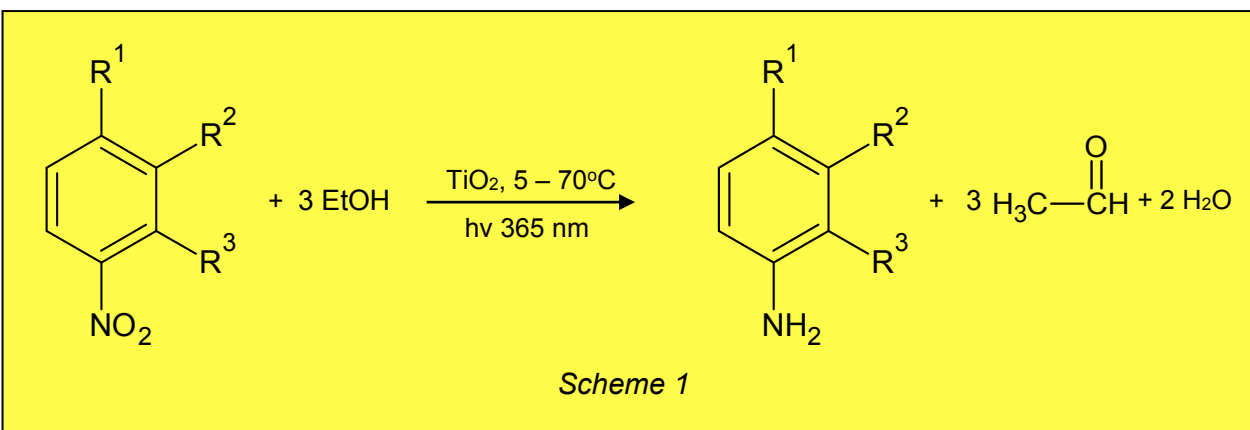


Application Note 42: Further photochemical hydrogenations of nitro compounds

Abstract

This application note builds upon the previous application note 41's green photochemical reductions. Extending the range of aromatic nitro compounds, including the hydrogenation of a Linezolid intermediate (Pfizer brand name Zyvox), and demonstrating excellent adaptability for the varying chemical properties. Vapourtec's efficient and precise generation 2 LED (Gen-2) was the sole light source used, allowing accurate and uniform 365 nm irradiation while providing impressive throughput. The optimized condition for each reduction was quickly achieved; residence time, concentration and reaction temperature were modified to maximize throughput while concurrently achieving close to 100% conversion to desired product. The aim of this work was to showcase the capability of the Vapourtec's E-Series when used in combination with the UV-150 photochemical reactor.



Background

The ability to optimise and scale reactions by continuous flow chemistry is well documented. The same approach can be applied to photochemical reactions in flow, but are less commonly known. Photochemistry can offer alternative, greener routes to a number of synthetic steps and open up other opportunities. Traditionally, in batch photochemistry, a sample would be irradiated for an excess duration to ensure completion. However, these methods can be problematic with any reaction where the product is not highly stable or side products are reactive. In these cases it is necessary to remove the product from the irradiated area soon after it has been formed. Once the reaction conditions are optimised, flow chemistry can overcome these. This is achieved due to:

- Uniform light exposure
- Controlled exposure times
- Temperature control
- Products formed being continuously removed from the reactor, reducing the chance of any side products forming or product absorbing radiation which would slow the reaction

In application note 41, it was shown that photochemical reduction of an aromatic nitro compound was possible in flow with the photo catalyst titanium dioxide pumped as a light slurry/suspension. Adapting and testing this method to a number of other nitro compounds, including highly reactive and 'real world' scenarios, was seen to be of great value towards photochemistry and to show the flexibility of Vapourtec systems with the UV-150 photochemical reactor. Application note 41 also demonstrated the comparable differences between mercury lamp, filtered mercury lamp and LED based light sources. In the past, LED light sources at 365 nm have had low efficiency lacking enough output to give adequate throughput, however the new Vapourtec Gen-2 LED proved that it can compete with mercury based light sources providing comparable throughput combined with double the efficiency and precise wavelength.

The compounds chosen for this app note are 4-nitroanisole, 2,4-dichloronitrobenzene, 4-(2-fluoro-4-nitrophenyl)morpholine (Linezolid intermediate) and the compound from app note 41, 3-nitroacetophenone. The resulting products of each nitro reduction are their corresponding aniline. Aniline compounds are synthetically important, a key building block used in many synthetic steps. The other functional groups present determine the reactivity of the aniline. This proved to be a significant factor to consider for this application note during optimisation.

Optimization

The aim of this work was to optimize a number photo catalyzed reductions of varying nitro compounds with different properties using TiO_2 to find the maximum throughput and show the adaptability of the UV-150 system to tailor reactions.

Setup

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

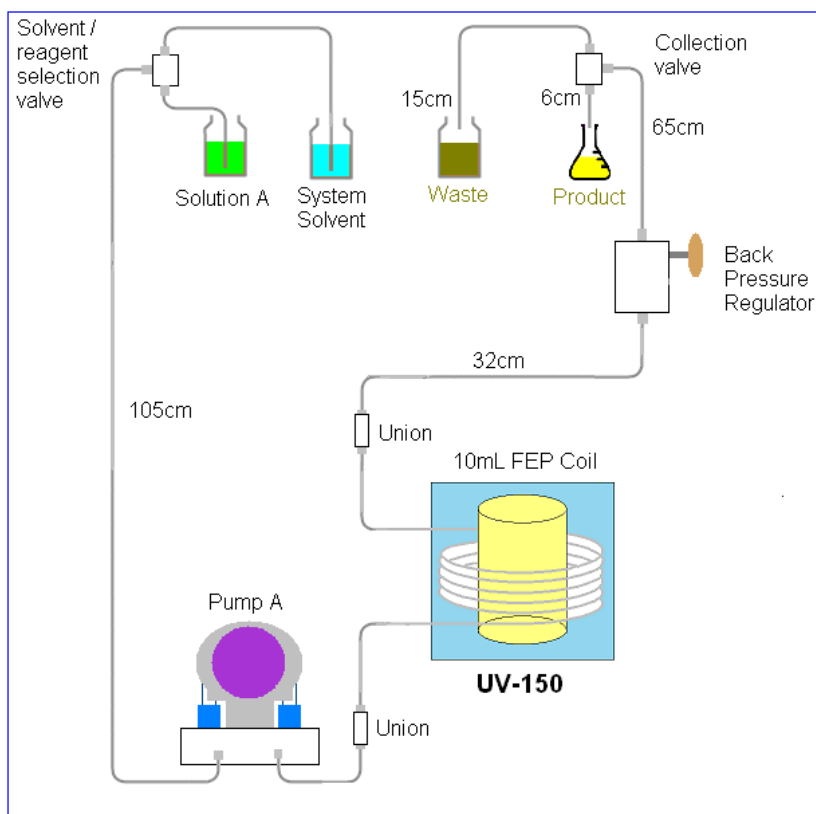


Fig.1

The UV-150 was fitted with a 10 mL reactor, a connecting tube in series and a manually adjustable back pressure regulator. The eluent was collected via the waste/collection switching valve.

Pump Tubing

The E-Series is fitted with two or 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. In this application note, flow rates above 10 mL/min were used. To achieve this, two pumps were used in unison, allowing a possible maximum flow rate of 20 mL/min.

The solvent used was ethanol, whilst being compatible with both tube types, V-3 pumps were used with the blue tubing in this study.

Reagents

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

Reagent A - 0.002M to 0.01M of selected nitro compound in ethanol (459884-1L) with 10 mg/ml TiO₂ (718467-100G).

System Parameters

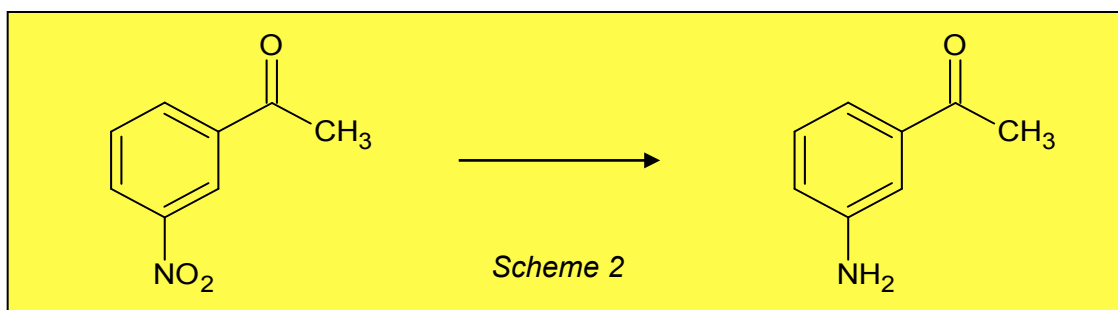
System solvent:	Ethanol
Solution A:	0.002M – 0.01M nitro compound in ethanol with 10mg/ml TiO ₂
UV Light Sources:	365 nm LED generation 2 (Gen-2)
Flow rate A:	1 - 20mL/min
Reactor volume:	10 mL reactor
Reactor temperature:	5 - 70°C
Back pressure regulator:	3 bar set with the variable BPR

The optimization process followed the sequence of steps listed below:

1. Priming the pumps with ethanol (EtOH):
The selection valve (or valves if flow rate > 10mL/min using 2 pumps) was set to 'Solvent' and the pump was primed with ethanol. This is done by selecting the prime function from the touchpad control. The priming process is fully automated.
2. Prepping the system
The reaction system was prepped with the easy-MedChem™ software using the flow-wizard option, where reaction conditions, flow rate and parameters were set and left for the lamp to turn on and the reactor reach desired temperature.
3. Reaction optimization:
A selective range of flow rates were run using the flow-wizard. Flow rates were varied between 1 - 20mL/min in a 10 ml reactor at variable temperatures. For each reaction, 16 mL of reagent A was input, discarding the first 7mL of the output, collecting the following 2mL and discarding the last 7mL. This was to ensure the collected product was representative of the steady state. During the reaction process, Reagent A was gently stirred to ensure the TiO₂ remained uniform throughout the reaction mixture.
4. Work-up and analysis:
The sample was filtered to remove TiO₂, diluted tenfold and analyzed by HPLC. The degree of conversion was assessed by the appropriate integration peaks.

Results and Discussion

3-Nitro-acetophenone to 3-amino-acetophenone

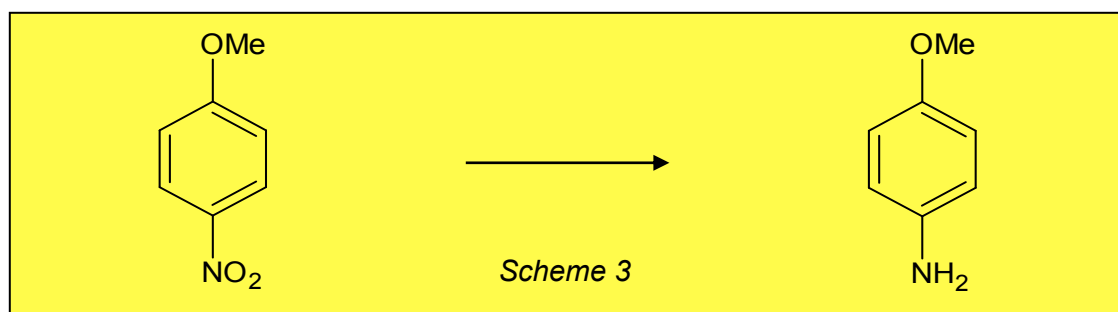


Reaction temp (°C)	Flow rate (ml/min)	Residence time (min)	Concentration (M)	Conversion to Product (%)
⁽¹⁾ 70	15	0.67	0.01	87
70	12	0.83	0.01	⁽²⁾ 99
70	10	1	0.01	99
70	6.7	1.5	0.01	99

(1) 70°C was chosen as throughput was found to be higher than at room temperature.

(2) Optimal time for full conversion was 45s. Work up resulted in pure 3-amino-acetophenone.

4-Nitroanisole to p-anisidine



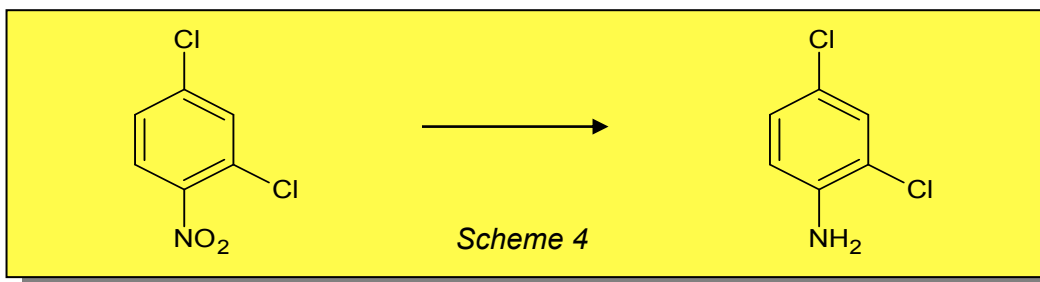
Reaction temp (°C)	Flow rate (ml/min)	Residence time (min)	Concentration (M)	Conversion to Product (%)
30	15	0.66	0.01	⁽³⁾ 81
30	5	2	0.01	⁽³⁾ 91
30	2	5	0.01	⁽³⁾ 91
5	20	0.5	0.01	49
5	15	0.66	0.01	59
5	10	1	0.01	81
5	6.66	1.5	0.01	⁽⁴⁾⁽⁵⁾ 99
5	5	2	0.01	⁽⁵⁾ 99

(3) Reaction temperatures above 5°C exhibited competing side reactions, conversion rates were lower.

(4) Optimal time for full conversion was 72s.

(5) Work up difficult due to competing side reactions with acetaldehyde.

2,4-Dichloronitrobenzene to 2,4-dichloroaniline

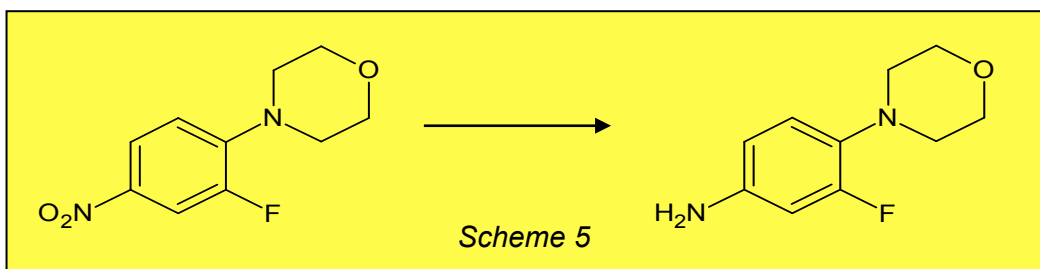


Reaction temp (°C)	Flow rate (ml/min)	Residence time (min)	Concentration (M)	Conversion to Product (%)
70	20	0.5	0.01	73
70	15	0.66	0.01	⁽⁶⁾ 99
70	10	1	0.01	99
70	10	1	0.02	⁽⁷⁾ 58
70	5	2	0.04	⁽⁷⁾ 52

(6) Optimal time for full conversion was 40s. Work up resulted in pure 2,4-dichloroaniline.

(7) Increasing concentration and residence time proportionally yielded a lower conversion, therefore did not improve throughput.

Linezolid intermediate, 4-(2-fluoro-4-nitrophenyl)morpholine to 3-Fluoro-4-(4-morpholinyl)aniline



Reaction temp (°C)	Flow rate (ml/min)	Residence time (min)	Concentration (M)	Conversion to Product (%)
⁽⁸⁾ 30	2.5	4	0.01	68
30	2	5	0.01	82
30	1.81	5.5	0.01	99
30	1.66	6	0.01	99
30	20	0.5	0.003	81
30	20	0.5	0.0025	92
30	20	⁽⁹⁾ 0.5	⁽¹⁰⁾ 0.002	⁽¹¹⁾ 99

(8) Reaction temperatures above 30°C exhibited competing side reactions, conversion rates were lower.

(9) Optimal time for full conversion was 30s.

(10) The concentration of 4-(2-fluoro-4-nitrophenyl)morpholine was decreased as it absorbs strongly, competing with the absorption of the catalyst TiO₂.

(11) Work up problematic due to competing side reactions with acetaldehyde.

Discussion and Summary

From the results, it is clear that two main factors affected the maximum possible throughput. First is the reactivity of the aniline product, the more reactive it is, the gentler the reaction conditions needed to be to prevent side reactions occurring. From the compounds tested, 2,4-dichloroaniline was the least reactive, followed by 3-amino-acetophenone, 4-(2-fluoro-4-nitrophenyl)morpholine and the most reactive being p-anisidine.

The second important factor is how strongly the starting materials and products absorb photons in the 365 nm wavelength relative to the titanium dioxide catalyst. Of the compounds used in this study, only 4-(2-fluoro-4-nitrophenyl)morpholine absorbed strongly. With this compound the rate of reaction was reduced due to hindering the absorption by titanium dioxide. The following table compares the throughputs obtained:

Compound	Optimal temperature (°C)	Optimal concentration (M)	Optimal residence time (s)	Throughput (g/hr)
4-nitroacetophenone	70 °C	0.01	45 s	1.05 g/hr
4-nitroanisole	5 °C	0.01	72 s	0.61 g/hr
2,4-dichloronitrobenzene	70 °C	0.01	40 s	1.46 g/hr
4-(2-fluoro-4-nitrophenyl)morpholine	30 °C	0.002	30 s	0.54 g/hr

The main challenges in the photochemical reduction was the potential for the reaction products (anilines) to react with the acetaldehyde by-product, undergoing nucleophilic substitution and possible aerial oxidations while in solution. The relatively unreactive anilines could be processed at room temperature and even above and then purified by removal of solvent and acetaldehyde by evaporation. The more reactive anilines required lower processing temperatures and additional work-up steps, such as the use of scavenger columns to remove the aldehyde. It is important to note that photochemical reduction in batch conditions would not be possible with reactive aniline products.

A summary of the key characteristics in the processing of each compound follows:

The reduction of 3-nitro-acetophenone was found to be quick and efficient at 70°C yielding complete conversion to 3-amino-acetophenone. HPLC analysis showed only a single peak, representing the 3-amino-acetophenone product with no impurities or side reactions present. Reacting at lower temperatures was unnecessary as there were no side reactions. Lower temperature resulted in slower rate of reaction. The solvent and side products were evaporated to yield solid 3-amino-acetophenone with no detectable byproducts.

p-Anisidine was found to be more reactive than the other anilines, readily reacting with the side product, acetaldehyde and further oxidizing. As a result, the reaction at 70°C, albeit faster, resulted in a number of side products. Lower temperatures were required to control the side-product formation. 30°C produced a fast reaction, however the highest conversion to product at 30°C was found to be 90%. While the reaction at 5°C was slightly slower there were negligible side products. Isolation of pure p-anisidine proved challenging, owing to competing side reactions between the product and acetaldehyde, likely forming a Schiff base. Further purification steps are necessary to obtain pure p-anisidine, we are still looking at this.

The reduction of 2,4-dichloronitrobenzene was quick and clean, with no trace of any side reactions even at 70°C. The reaction was significantly faster than 3-nitro-acetophenone. To investigate a possible method of increasing throughput, the concentration was increased. At double the concentration and residence time, the mol/min would be the same; however the conversion ratio had decreased. It is assumed the increased concentration limited the TiO₂ absorption, lowering conversion. 2,4-dichloroaniline was isolated in a pure form by evaporation.

When reducing 4-(2-fluoro-4-nitrophenyl)morpholine the reactivity of the product was between that of 3-nitro-acetophenone and 4-nitroanisole. At 70°C there were a number of side reactions occurring. Decreasing the temperature to 30°C was found to be optimal with no evident side reactions. The compound absorbed very strongly at 365 nm, a possible reason for the slower reaction time observed compared to all previous nitro compounds. To compensate, the concentration was decreased, this increased the throughput whilst still achieving full conversion. Isolation of pure 3-fluoro-4-(4-morpholinyl)aniline proved challenging, with side-reactions similar to that of p-anisidine. One approach under consideration is to 'trap out' the aniline by reacting it straight through into the next step of the Linezolid synthesis.

Conclusion

This application note demonstrates that the Vapourtec E-Series with V-3 pumps and UV-150 photochemical reactor are more than capable of optimising and scaling the photo induced reductions of a variety of aromatic nitro compounds having varying properties. Using the Linezolid intermediate, 4-(2-fluoro-4-nitrophenyl)morpholine, we have shown that this method using titanium dioxide as a photo catalyst in continuous flow can be applied to a step in the synthesis of an important drug compound. We argue that this note shows the broad applicability of photochemical nitro-reductions together with the versatility of modern flow chemistry systems.