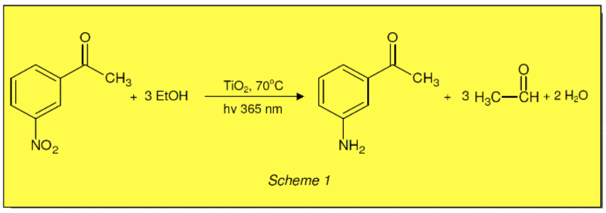
Application Note 41:

Photochemical hydrogenation of 3-nitroacetophenone

Produced by Vapourtec

Abstract

This application note demonstrates a green photochemical route to the reduction of nitro compounds. The powerful combination of Vapourtec's V-3 pump and the UV-150 photochemical reactor are utilized to deliver the photo catalyst as a slurry and provide precise control over the continuous flow photochemical reaction, even with short reaction times of less than 1 minute. The TiO_2 photo catalyst is safe, cheap and simple to remove by filtration. We also present a fascinating comparison of the performance of three different 365 nm light sources; filtered mercury lamp, LED Gen-1 and LED Gen-2. The Gen-2 LED achieved comparable throughput to the mercury lamp while consuming <50% of the power.



Scheme 1

**See Mahdavi et. al. for suggested reaction mechanisms*

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Background

Although photochemistry is not a new science, its application in pharmaceutical and fine chemical manufacture has been limited, in part due to the lack of suitable equipment (especially at scale), but also due to poor efficiency for traditional batch reactors. The synergy of flow and photo chemistry offers greater benefit. Achieving uniform UV exposure in batch reactors is difficult, even if reactants are agitated. With flow chemistry, reactants are continuously passed by the UV source, removing product from the irradiated area thus providing greater control and consistency, both in resultant compound and reproducibility.

Recent developments in LEDs also offer huge potential for improving outcomes in photochemistry. High efficiency UV LED technology, particularly at longer wavelengths used in catalyst mediated reactions (350 to 550 nm), allow the source wavelengths to be tuned to the application. Reaction yield and selectivity are improved, as well as reducing waste heat and power consumption when compared to traditional mercury lamp technology. LEDs are safer in use, easier to maintain and, unlike mercury lamps, can be used safely at scale without recourse to sophisticated inert gas blanketing systems for the mercury lamp.

Conventional hydrogenations, such as catalytic hydrogenation on metals or homogeneous catalysis using metal complexes are common reactions in organic chemistry. An alternative approach to hydrogenation is presented in this application note using TiO_2 as a photo catalyst, which offers a green alternative to produce the corresponding amines.

The benefits include:

- The use of ethanol as both the solvent and hydrogen source.
- The use of an easily removable, cheap and very safe catalyst, TiO_2, commonly found in many commercial products, such as toothpaste, sunscreen and paints.
- From an API standpoint, the exclusion of transition metal catalysts from the reaction is a major benefit whereas in traditional hydrogenation methods the removal of trace amounts of transition metal catalysts is expensive, tedious and difficult.
- Reaction conditions used in photo catalytic TiO_2 reductions only require mild conditions, opening further possibilities in other compounds which contain other reducible functional groups.

Photo catalyzed nitro reductions have previously been published under batch conditions leading to a time consuming and somewhat inefficient process. Some methods for this reaction in batch include stirring a suspension of TiO_2 with continuous exposure to a UV lamp in excess of many hours. However, if continuous flow chemistry is applied, the advantages to scale reactions and rapidly determine optimized conditions, which have been well documented, could further improve efficiency for this reaction and decrease the reaction time greatly.

Vapourtec's easy-Photochem system was used to undertake this reaction. This photo catalytic reaction requires pumping of a light slurry with continuous UV radiation, which can be achieved with the Vapourtec V-3 pump and UV-150 reactor respectively.

UV radiation can be applied via the UV-150 reactor using a number of different light sources. A mercury lamp with the use of different filters is a very versatile method as the wavelength of the light reaching the reaction can be changed and controlled. However, the continuing development of LEDs offers a new and more energy efficient light source option. Further, the wavelength emitted can be finely controlled with LEDs, helping minimize risk any side reactions at other wavelengths, something some filters with mercury lamps cannot ultimately do.

This application note demonstrates the use of the easy-Photochem system and documents the following:

- The use of a photochemical reaction to provide a green and cost effective route to the reduction of 3-nitroacetophenone to 3-aminoacetophenone.
- The ability of the easy-Photochem's V-3 pumps to deliver TiO_2 as a slurry.
- The performance of mercury lamp when compared to modern LEDs operating at 365 nm.

Optimization

As stated above, the aim of this work was to optimize a photo catalyzed reduction of a nitro compound using TiO_2 and find the minimum required exposure time for complete conversion using different light sources, including 2 mercury lamp filters, generation 1 LEDs (Gen-1) and the new generation 2 LEDs (Gen-2).

Setup

The flow reactor was set up using the E-Series pump module as shown in Fig 1.

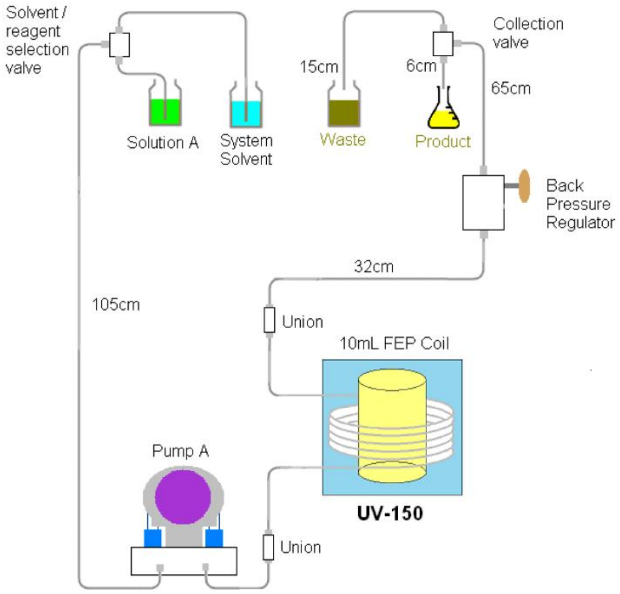


Fig 1

The UV-150 was fitted with a 10 mL reactor, a connecting tube in series and a manually adjustable back pressure regulator. The elution outflow 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 the blue tubing in this study.

Reagents

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

Reagent A - 0.01M 3-nitro-acetophenone(N9381-100 G) in ethanol(459884-1L) with 10 mg/ml TiO_2(718467-100 G).

System Parameters

System solvent:	Ethanol
Solution A:	0.01 M 3-nitro-acetophenone in ethanol with 10 mg/ml TiO_2
UV Light Sources:	Medium pressure Hg lamp set to full power, gold filter no.4 used Medium pressure Hg lamp set to full power, blue filter no.2 used LED generation 1 LED generation 2
Flow rate A:	1 – 20 mL/min

Reactor volume:	10 mL reactor.
Reactor temperature:	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 > 10 mL/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-Scholar™ 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 to 70 °C.
3. *Reaction optimization:*
   A selective range of flow rates were run using the flow-wizard. Flow rates were varied between 1 – 20 mL/min in a 10 ml reactor at 70 °C. For each reaction, 16 mL of reagent A was input, discarding the first 7 mL of the output, collecting the following 2 mL and discarding the last 7 mL. This was to ensure the collected product was representative of the steady state. During the reaction process, the sample vial was gently stirred to ensure the TiO_2 slurry in reagent A was kept uniform.
4. *Work-up and analysis:*
   The sample was filtered to remove TiO_2, diluted tenfold and analyzed by HPLC. The degree of conversion was assessed by the appropriate integration peaks and ^{1}H-NMR spectroscopy ($CDCl_3$) was used to confirm product integrity.

Results and Discussion

Ethanol and photon requirement

For the reduction of the nitro compound to occur the excitation of electrons and the presence of an alcohol are required, allowing the reduction to occur with the oxidation of the alcohol and production of hydrogen. Reduction of one nitro molecule requires six photons, as are six equivalents of ethanol to produce acetaldehyde, water and hydrogen. As a result, ethanol was used as the solvent, to allow a large excess for optimal reaction conditions. Even with a large photon requirement, the reaction in flow is very efficient, with some reactions occurring in less than one minute, shown in table 1.

Concentration of 3-nitro-acetophenone

Initial experiments focused on finding the optimum concentration of the starting material and TiO_2. TiO_2 acts as a catalyst in this reaction. It was found that 10:1 TiO_2: 3-nitroacetophenone was optimal. For this hydrogenation to progress rapidly and efficiently it is important that the TiO_2 absorbed the photons much more strongly than the starting material or any products / intermediates formed during the course of the reaction. Experiment number 13 in table 1 shows this aspect, using only half the TiO_2 and five times the concentration of starting material, even left for a long reaction time of ten minutes, the yield is far from ideal.

Table 1

Exp (no.)	Light source	Flow rate (ml/min)	Exposure time (min)	Conc. of starting material (M)	Concentration of TiO_2 (mg/ml)	Conversion (%)
1	Mercury filter 4	5.0	2.0	0.01	10	100
2	Mercury filter 4	6.7	1.5	0.01	10	100
3	Mercury filter 4	10.0	1.0	0.01	10	77
4	Mercury filter 2	10.0	1.0	0.01	10	100
5	Mercury filter 2	20.0	0.5	0.01	10	96
6	LED 1	2.5	4.0	0.01	10	100
7	LED 1	2.8	3.5	0.01	10	100
8	LED 1	3.3	3.0	0.01	10	88
9	LED 2	6.7	1.5	0.01	10	100
10	LED 2	10.0	1.0	0.01	10	100
11	LED 2	12.0	0.83	0.01	10	100
12	LED 2	15.0	0.67	0.01	10	87
13	Mercury filter 4	1.0	10.0	0.05	5	37
14	None	1.0	10.0	0.01	10	0
15	Mercury filter 4	1.0	10.0	0.01	0	0

Mercury lamp and LED comparison

For each light source, reagent A was processed a number of times at increasing flow rates, and therefore decreasing exposure times. The reaction times were continuously reduced until the reaction did not achieve 100% conversion. Recording the integration values for each peak from HPLC data, the optimum reaction time for each light source was calculated, allowing for the total throughput per hour and reaction efficiency to be known.

Table 1 shows the raw data obtained. It is important to note that filter 2 allows a larger range and intensity of light than filter 4 while the LED emissions have a narrow range, but broader peak. The spectroscopic data for these three filter systems is shown below.

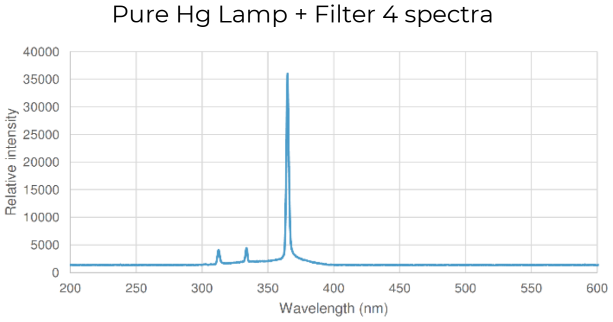


Fig 2

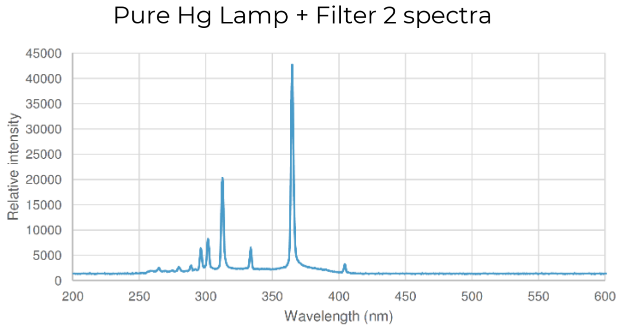


Fig 3

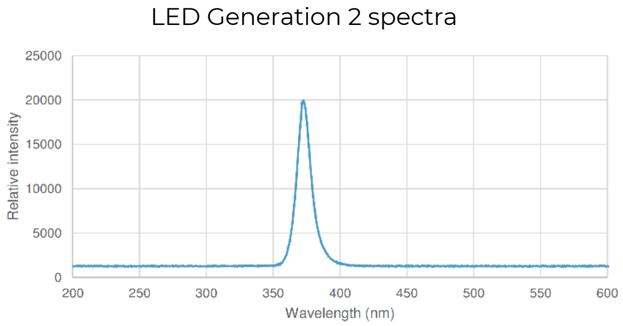


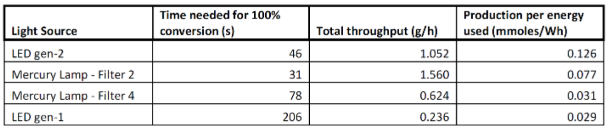
Fig 4

Figure 2 shows mercury lamp filter 4 spectra, which has very little emission of light other than wavelength of 365 nm. Figure 3 shows mercury lamp filter 2 spectra, which has greater emission of both 365 nm and other wavelengths. Figure 4 shows the LED gen 2 spectra, which is identical to LED gen 1. It shows only a single, broad peak, from 360 nm to 380 nm with no other wavelengths.

While other wavelengths do reach the reactor with the mercury lamp and filters, checking HPLC and NMR data, the evidence clearly suggests that there are no side reactions occurring in a quantifiable amount to affect the results. As for the spectroscopic data for the LED sources, the slightly broader range of wavelength also does not contribute to any additional side reactions.

From the data obtained, it is clear that the advancements in LED technology are constantly improving. Not only does the LED generation 1 and 2 offer more precise wavelengths, the improvement for generation 2 can give a reaction time close to that of a mercury lamp with a nonspecific filter. However, in terms of energy efficiency, the LED lamps use just over one third of the power usage, with the mercury lamp requiring 150 W, the LED gen 1, 60 W and the LED gen 2 requiring 62 W.

Table 2



Light Source	Time needed for 100% conversion (s)	Total throughput (g/h)	Production per energy used (mmoles/Wh)
LED gen-2	46	1.052	0.126
Mercury Lamp - Filter 2	31	1.560	0.077
Mercury Lamp - Filter 4	78	0.624	0.031
LED gen-1	206	0.236	0.029

Table 2 shows the summarized data for each light source as well as the optimal time for 100% conversion, total throughput and efficiency. As shown, whilst the mercury lamp with filter 2 does give a higher throughput, its efficiency is lower than LED gen 2.

Control Experiments

Two further reactions were run to confirm the methodology and to show no secondary reactions were occurring. The first was with no light, the reaction vessel, temperature and reagent A was kept the same and the flow rate was set to 1 mL/min, allowing for a longer 10 min exposure time. This resulted in no reaction (see exp no.14 in table 1). The second was with no TiO_2, a new 10 mL reactor was used to eliminate any possibility of residual TiO_2. The temperature and concentration of 3-nitro-acetophenone was kept the same. Again a slower flow rate of 1 mL/min was used for a 10 min reaction time. Again no reaction occurred (see exp no.15 in table 1).

Conclusion

The work described in this report demonstrates that the Vapourtec E-Series is capable of carrying out photo catalyzed reduction of 3-nitro-acetophenone compounds safely and efficiently in a continuous manner. It also highlights the capability of the E-Series to pump light slurries. It compares the relative performance between a mercury lamp with two different filters against LEDs and demonstrates the recent advancements in efficiency of LED technology. Further, it shows that an E-Series is capable of rapidly finding the optimal exposure for a photochemical reaction, allowing minimal power consumption, improving the reactions green credentials.

Further work is underway to establish the scope of this reaction methodology, applying the technique for the reduction of a range of different Nitro Compounds.

References

Farah Mahdavi, Thomas C. Bruton, and Yuzhuo Li, *J.Org. Chem*., **1993**, 58, 744-746