PHOTOCUBE

PERFORMING THE THIOL-ENE CLICK REACTION IN A PHOTOCUBE

INTRODUCTION

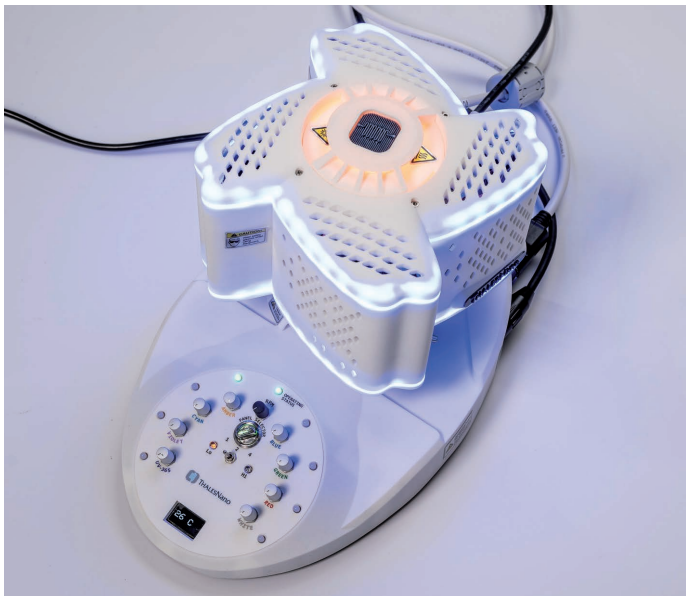
„Click" reactions are highly versatile tools for chemists and researchers working in synthesis. **Rapid reaction rate, robustness** and **high atom efficiency** are all key aspects in the popularity of these reaction types. In 2022, the Nobel Prize in chemistry has been awarded to Professors Barry Sharpless, Morten Meldal, and Carolyn Bertozzi for their pioneering research on click reactions and bioorthogonal transformations. Click chemistry principles cover a wide range of reaction types such as the **alkyne-azide addition** ("CuAAc"), **sulphur-fluoride exchange** ("SuFEx"), **photo-initiated thiol-ene addition**, and more that are facilitated by performing them under continuous flow conditions[1].

Researchers at University of Debrecen have conducted impressive research on thiol-ene click reactions utilizing the capabilities of ThalesNano's PhotoCube reactor. We hereby discuss the results of the Master's Thesis originally written in Hungarian[2], as well as present our own research data on the topic highlighting **improved reaction rate** while using continuous flow compared to batch procedures.

INSTRUMENTATION AND SAFETY CONSIDERATIONS

Performing photochemical reactions under batch and continuous flow conditions is streamlined using the **PhotoCube**. The reactor's innovative design allows **illuminating samples** with **multiple wavelengths of light** simultaneously. The 4 sides of the reactor chamber house the **LEDs** with the following available wavelengths: **365, 395, 457, 500, 523, 595, 623 nm**, and **white**. The PhotoCube was designed with continuous **flow** and **batch operation** in mind. The reactor can support **four 25 mL vials** or **eight 4 mL vials** during batch operation. Connecting a **syringe pump** or **HPLC pump** to a loop placed inside the reactor allows **continuous flow operation** at a wide range of residence times or the option of stop-flow operation. Converting the reactor space from batch to flow is designed to be easy and quick with the PhotoCube's **proprietary loop** and **vial holders**.

Batch reactions are aided by the **built-in magnetic stirring function** for which the stirring rate can be conveniently adjusted through a **potentiometer** located on the separate controlling panel of the instrument. The number of illuminated panels is user determined from the panel as well, where the light sources and light intensities can also be fine-tuned. The instrument's **"Hi" mode** allows a **single light source** to be used **up to 300 W power**, in **"Lo" mode multiple wavelengths** can be used simultaneously. Cooling of the instrument is supported by the built-in fans, which can be further improved by connecting an external chiller to its ports. The display located at the bottom of the control unit provides useful data about the operational parameters of the instrument such as reaction chamber temperature, LEDs in use and their respective power values in percentage.

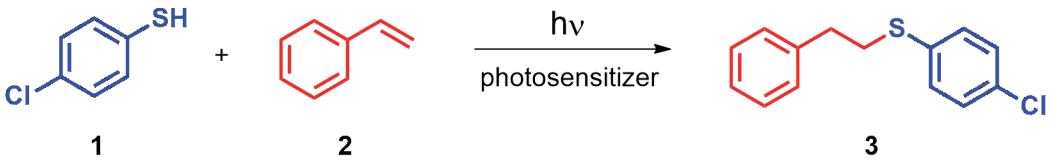


A **safety trigger** located at the top of the reactor chamber will automatically shut off the LEDs once the cap of the chamber is removed or not in place correctly, preventing accidental user exposure to high intensity light.

DISCUSSION AND RESULTS

Balázs Nagy et. al investigated **photo-initiated thiol-ene click reactions** on various substrates under **batch** and **continuous flow** conditions using the PhotoCube.

The researchers chose the **thiol-ene** addition between **4-chlorobenzenethiol** (**1**) and **styrene** (**2**) as a model reaction for optimization and parameter screening (Scheme 1). **Batch screening** was carried out using 100 mg (0.96 mmol) styrene (1), 166 mg (1.154 mmol, 1.2 equiv) 4-chlorobenzenethiol (**2**) in 2 mL of each screened solvent (chloroform, acetonitrile, toluene, methanol, hexane, dichloromethane, ethyl-acetate, acetone). To illuminate the reactor zone, **457 nm, 625 nm, 395 nm** wavelengths were attempted.



Scheme 1: Model reaction between 4-chlorothiobenzene (**1**) and styrene (**2**)

Reactions were carried out both in the **absence** and **presence of photocatalysts** such as $Ru(bpy)_3(PF_6)_2$, DPAP, eosin Y, methylene blue, acridine orange. Each vial **was illuminated for 40 minutes** with **periodical sampling** during the reaction. Conversion and sample composition were determined using **GC-MS analysis**.

Blue LED (**465 nm**) illumination showed **>75% conversion** for all solvents, out of which **toluene** performed the best with **>90%** conversion. In the case of **395 nm light, conversions were lower** in general, **MeOH** showed **linear conversion tendency** vs time. **Red illumination** (625 nm) required **photosensitizing**, with **MeOH** proving to be the most ideal solvent with **60% conversion**. From the solvent screening optimizations, **methanol** turned out to be the overall **best performing solvent** thanks to the lack of pre-activation behaviour, rapid reaction rate and good conversion (Figure 1).

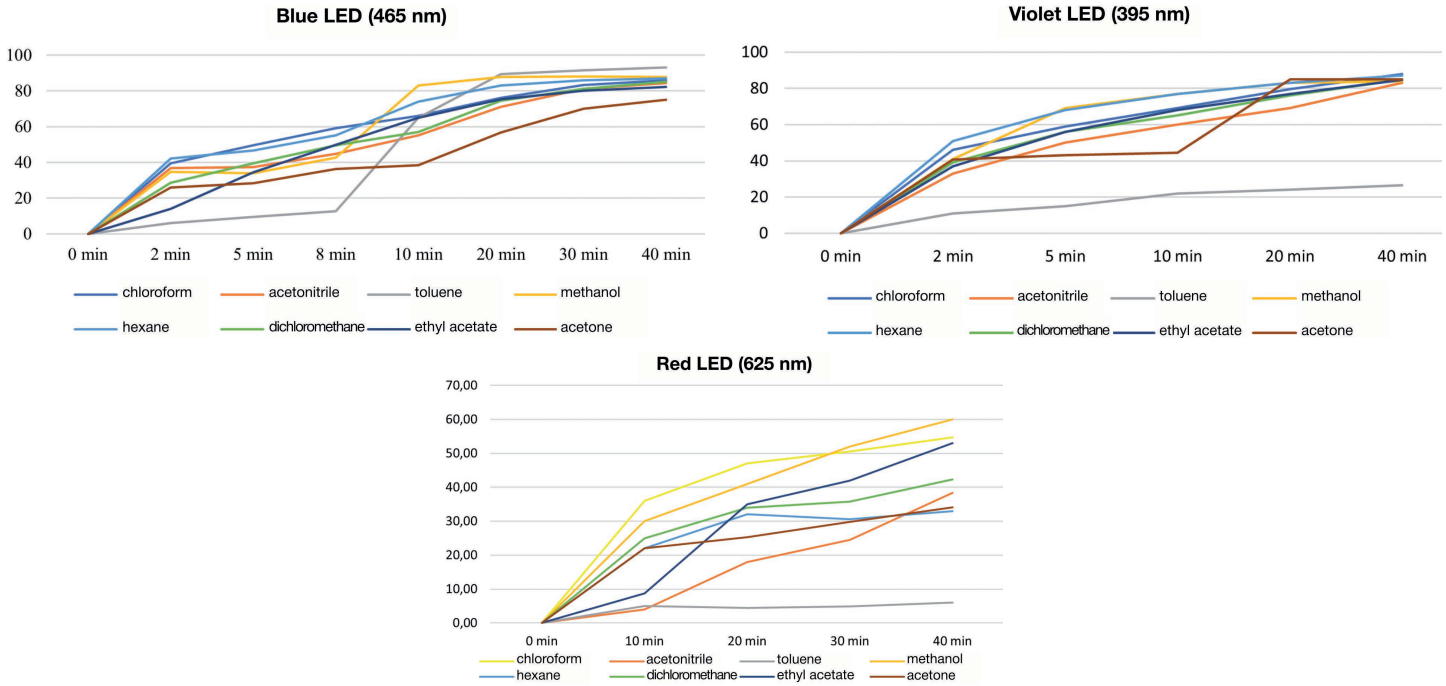
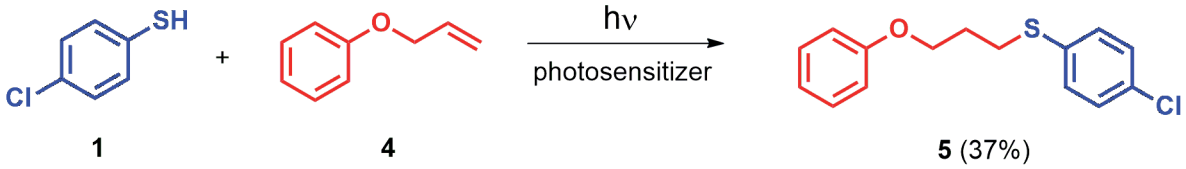


Figure 1: GC yields of 3 using different solvents and wavelengths

Photosensitizer screening was performed in **batch, 30 minutes illumination**, using **MeOH** as solvent. Interestingly, results showed that by using **photosensitizers**, neither the **conversion** nor the r**eaction rate** improved compared to the reactions without the addition of these.

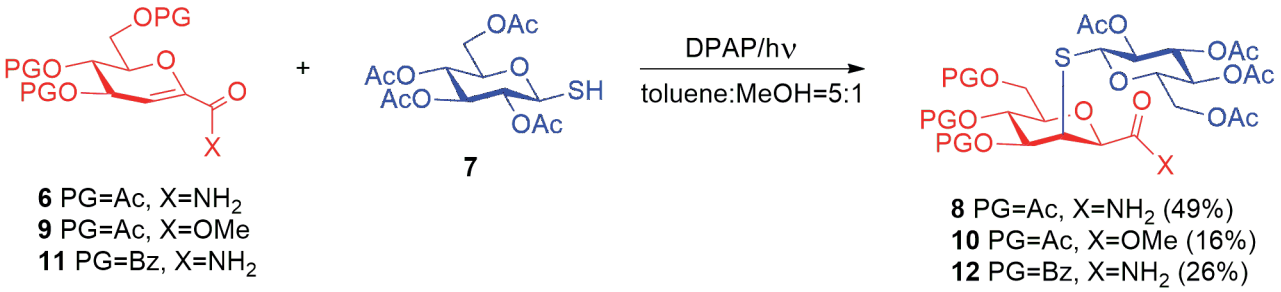
The researchers carried out the thiol-ene reaction using **allyl phenyl ether** (**4**) and the same reagent **4-chlorobenzenethiol** (**1**) as before with **37% isolated yield** (Scheme 2).



1 **4** **5** (37%)

Scheme 2: Thiol-ene click reaction of 4-chlorothiobenzene (1) and allyl phenyl ether (4)

Most importantly, the team used the PhotoCube to synthesize various carbohydrate derivatives following the **optimization experiments** (Scheme 3). **Blue illumination**, coupled with **DPAP photoinitiator** yielded in the desired disaccharides products **8**, **10** and **12**. Comparing the results to the research group's **home-built reactor** (UV-A/UV-C) the **blue LED** of the **PhotoCube** provided equal results while being **safer** and **more convenient** in terms of **multi-wavelength** and **light-intensity fine-tuning**.



6 PG=Ac, X=NH_2
9 PG=Ac, X=OMe
11 PG=Bz, X=NH_2

7

8 PG=Ac, X=NH_2 (49%)
10 PG=Ac, X=OMe (16%)
12 PG=Bz, X=NH_2 (26%)

Scheme 3: Thiol-ene click synthesis of disaccharides

Thanks to the simple **convertability** from **batch** to **continuous flow mode** in the PhotoCube, **reaction kinetics studies** were carried out in both HI and LO modes of batch operation and in continuous flow HI mode. The reaction mixture contained both **1** and **2** in 0.05 M concentration, **reaction time** in **continuous flow** was adjusted through the **HPLC pump flow rate**. Conversion was followed using **thin layer chromatography**. Figure 2 shows the **reaction time** to **full conversion**; error bars were determined from 3 separate samples for each condition. Reaction rate improvements were observed at higher intensities. The **continuous flow experiments** yielded **quicker results** compared to the batch procedures.

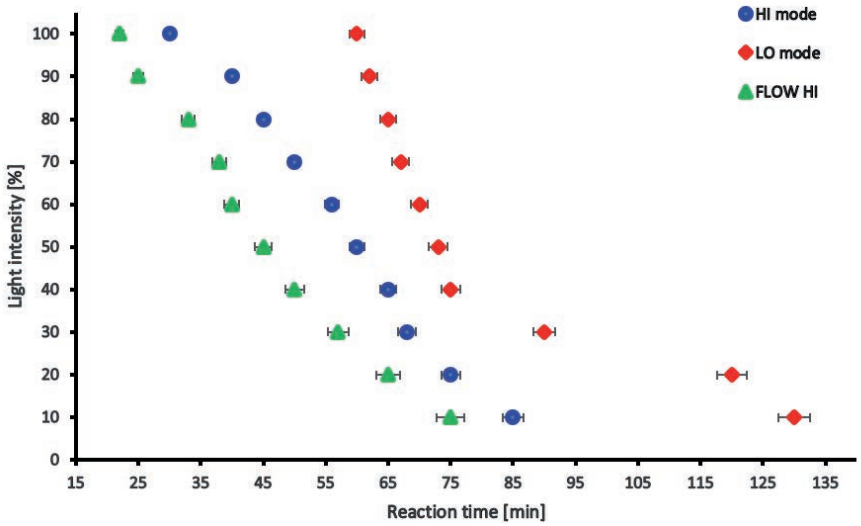


Figure 2: Batch and Flow comparison of reaction times

SUMMARY AND CONCLUSION

The research presented in this application note, together with our own experimental data, demonstrates the **versatility of the PhotoCube** for **photoinitiated thiol-ene click reactions**. Its **dual functionality** in both batch and flow processes, **high-intensity light outputs**, and **user-friendly interface** collectively contribute to significantly streamlining photochemical workflows for researchers.

REFERENCES

[1]Nándor Kánya, Tamás Sándor Zsigmond, Tamás Hergert, Klára Lövei, György Dormán, Ferenc Kálmán, and Ferenc Darvas, Click Reactions Meet Flow Chemistry: An Overview of the Applications of Click Chemistry under Continuous Flow Conditions, *Organic Process Research & Development* **2024** 28 (5), 1288-1307.

[2]https://dea.lib.unideb.hu/items/d4e7e161-2f3c-4f61-851c-7119818c1d26

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