APPLICATION NOTE 1

The performance of the Signify light engine - HANU reactor combination for a pharmaceutically relevant benzylic bromination reaction

Data courtesy of Ajinomoto Omnichem,
authored by Dr. Bert Metten and Peter Li

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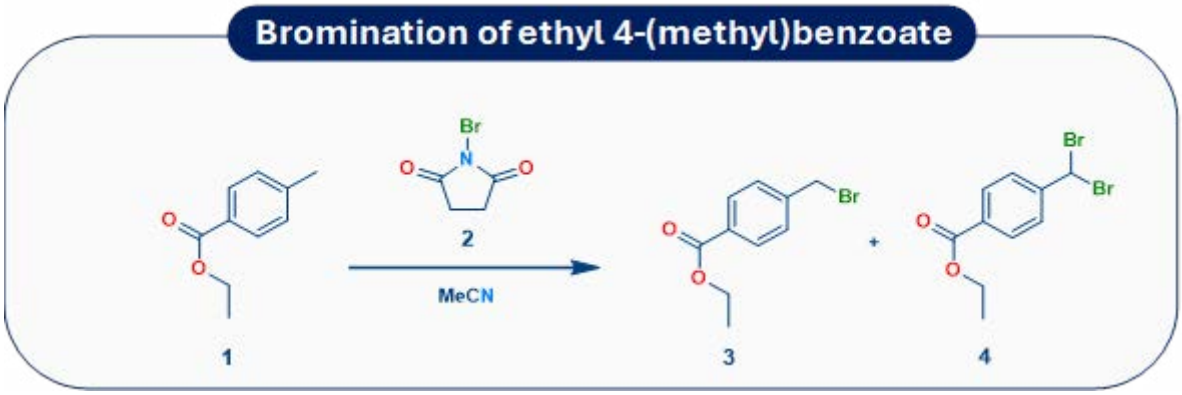
1. Abstract

The Wohl–Ziegler Bromination of ethyl toluate was performed in the **HANU™ reactor** in order to investigate the performance of the **Signify multi-color light engine**. The outcome of the combination was compared to the DART reactor – custom Kessil PR160L 400nm combination.[1]



Scheme 1. Wohl–Ziegler Bromination of ethyl toluate

2. Background

Halogenations like this benzylic bromination are the most scaled photochemical reactions in pharmaceutical development.[2] A very nice example was recently published.[1] The importance of mixing (Grotthuss–Draper law) as a key parameter was discussed. Furthermore, complete light saturation at high intensities was mentioned to allow an entirely reagent limited kinetic regime. The HANU reactor allows good dynamic mixing and the Signify light engine can provide high intensities and allows fast screening thanks to the built in flexibility.

Figure 1. Lab set-up at Ajinomoto BioPharma Services

The HANU™ reactor is a flow reactor equipped with a transparent window covering the entire process channel in order to allow irradiation of the reaction mixture and drive photochemical reactions. Good mixing is induced by pulsatile flow and is used to increase the film refreshment near the light source, in this case the very powerful Signify multi-color light engine.

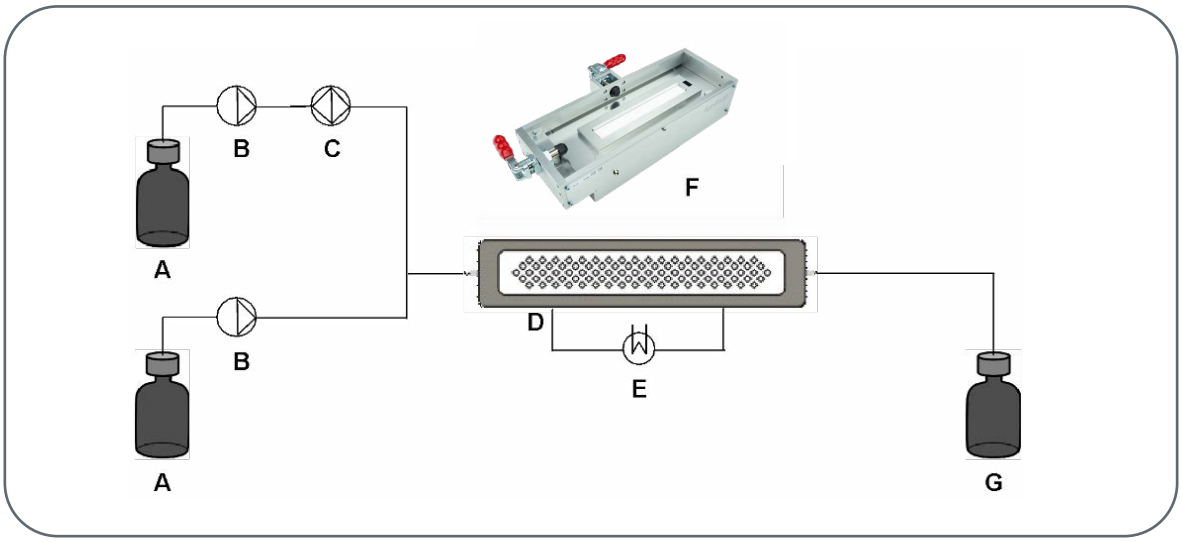
[1] Pratley, C.; Shaalan, Y.; Boulton, L.; Jamieson, C.; Murphy, J. A.; Edwards, L. J., Development of a Horizontal Dynamically Mixed Flow Reactor for Laboratory Scale-Up of Photochemical Wohl–Ziegler Bromination. Org. Process Res. Dev. 2024, 28, 5, 1725–1733.

[2] Moschetta, E. G.; Cook, G. C.; Edwards, L. J.; Ischay, M. A.; Lei, Z.; Buono, F.; Lévesque, F.; Garber, J. A.; MacTaggart, M.; Sezen-Edmonds, M., Photochemistry in Pharmaceutical Development: A Survey of Strategies and Approaches to Industry-wide Implementation. Org. Process Res. Dev. 2024, 28, 4, 831-846.

3. Experiment

3.1 Setup

The setup with the HANU™ reactor is depicted in Scheme 2. The HANU™ reactor assembly (Model: HANU 2X 5 inlay, cubic 2x2) consists of a baseplate that includes cubic static mixing elements with an integrated heat-exchanger to thermostat, a total reactor volume of 5 mL, and is made of stainless steel 316L, borosilicate window and ePTFE gaskets. The HANU™ reactor was connected to a Huber Petit Fleur thermostat circulating thermal oil at 20°C. The water-cooled Signify multi-color light engine was equipped with 365, 395, 420 and 450 nm LED's. For electrical power and optical power for each wavelength see **Table 1**.



A. Recipients with starting material
B. Metering pumps
C. Pulsator
D. HANU™ reactor
E. Circulation thermostat
F. Photochemistry Linear Light Engine (PLLE)
G. Recipient with crude product

Scheme 2. Setup of the experiment

3.2 Procedure

A first recipient, covered from light, was filled with 0.5 molar solution containing (16.42 g, 1 equiv.) and N-bromosuccinimide (18.80 g, 1.05 equiv) in acetonitrile (200 mL), a second recipient was filled with 250 mL acetonitrile. The reactor was purged with acetonitrile. Then, the two flows, respectively pumped equimolar at 99% and 1% of the required flow rate to obtain the target residence time τ (e.g. 5 ml.min-1 for τ = 1 min), were mixed via a T-piece prior to entering the HANU™ reactor. The pulsation frequency was 3 Hz and center-to-peak amplitude in the reactor 2.1 mm. The reaction was performed at 20 °C. After eluting three residence volumes (15 mL), the reaction mixture was collected in dark vials and prepared for HPLC analysis to identify and quantify the product. The product was isolated and purified according to the procedure described by Pratley et al.1 600 mL of collected reaction mixture resulted in 32.72 g, 40 mol% of white crystalline powder with >95% purity.

3.3 Results

A first screening of 4 different wavelengths was conducted in less than 30 minutes with a residence time of 1 min and 90% intensity. This afforded a clear chemical optimum at 395 nm under these conditions (see **Figure 2**). The 395 nm was also an overall good choice when one looks at the yields versus power (see Table 1 for yield per Watt). Also a quick screening of the effect of light intensity was possible. The intensity of the 395nm LED was applied at respectively 100-75-35-10-0% of the total power (see **Figure 3**).

Peak wavelength	365	395	420	450
P (W) electrical at 100%	99,8	82,4	89,7	73,3
P (W) optical at 100%	33	35,1	34,3	39,2
Yield (%)	85	90	88	83
Yield/W (opt)	2,58	2,56	2,57	2,12
Yield/W (elec)	0,85	1,09	0,98	1,13

Table 1. Relation power and yield

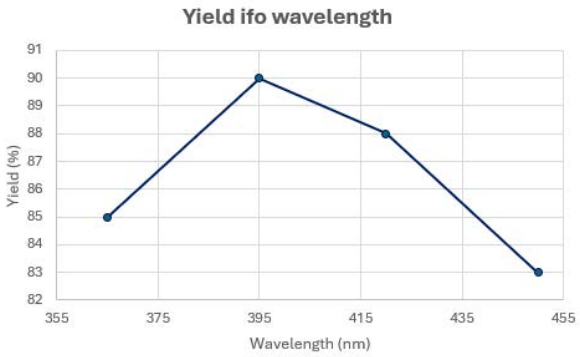


Figure 2. Yield in function of wavelengths

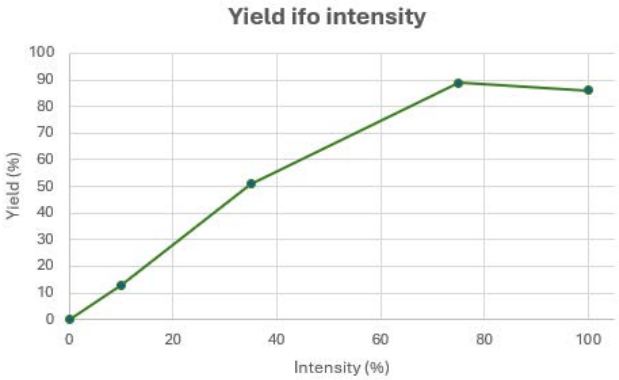


Figure 3. Yield in function of intensity

After the optimal wavelength was found, it was chosen to run this reaction for four hours (240 min) at 395 nm and 90% intensity, collecting samples every 30 minutes. HPLC analysis showed that good and stable conversions could be obtained (see Figure 3), albeit with fluctuating in situ ethyl-4-(bromomethyl)benzoate yields - the lowest yield being 80% and the highest 92%. Remarkably, no specific clogging occurred in contrast to the results in the DART reactor.1 Moreover, no brown oily film was observed on the reactor wall, which significantly reduced conversion in the DART reactor despite mechanical mixing. The latter reactor had to be dismantled for cleaning in less than 180 min. The HANU reactor did not show clogging nor fouling and remarkably very little signs of corrosion on the stainless steel surfaces. After this durance test, ethyl-4-(bromomethyl)benzoate was also isolated from the sample mixture (*vide supra*).

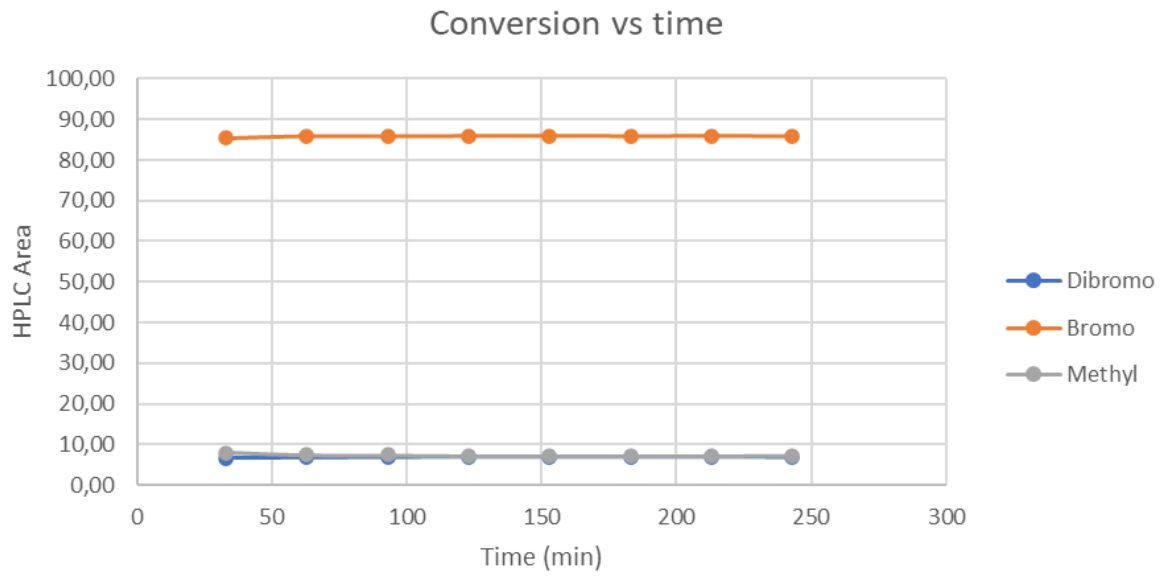


Figure 4 . Conversion over 240 minutes

4. Conclusion

The combination of the Signify multi-color light engine and the HANU flow reactor delivered promising results in the Wohl–Ziegler Bromination of ethyl toluate. A fast and easy screening led to the optimal wavelength (395 nm) and intensity (90%) as it offered the highest yield of ethyl-4-(bromomethyl)benzoate for a residence time of 1 minute. Furthermore, an endurance test was performed indicated no clogging or deposition of an oily film after continuously production for four hours, outperforming the previous published1 results. The space-time-yield based on the isolated yield (40% yield @395 nm with a residence time of 1 minutes) was approximately 3.3 times higher than in the dynamic mixed reactor (DART). The unoptimized work-up afforded 16.36 g*h-1 isolated product yield (40 mol%) in a 5 mL reactor.

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For more detailed information about the light source, please contact Signify at **remy.broersma@signify.com**.

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