ARTICLE

A Detailed Study of Irradiation Requirements, Towards an Efficient Photochemical Wohl-Ziegler Protocol in Flow

Holly E. Bonfield,[a] Jason D. Williams,[a][b] Wei Xiang Ooi,[a] Stuart G. Leach,[a] William J. Kerr[b] and Lee J. Edwards*[a]

Dedicated to the memory of Dr. Matthew P. John

Abstract: A platform has been developed to enable standardization of light sources, allowing consistent scale-up from high throughput screening in batch to flow, using the same pseudo-monochromatic light source. The impact of wavelength and light intensity on a photochemical reaction was evaluated within this platform, using the Wohl-Ziegler benzylic bromination of 4-methyl-3-(trifluoromethyl)benzonitrile with *N*-bromosuccinimide as a model system. It was found that only 40% of the maximum light intensity was required whilst still maintaining reaction rate, allowing more reliable temperature control and lower energy consumption. The optimized reaction conditions were subsequently applied to a range of synthetically relevant (hetero)aromatic compounds under continuous conditions, exploring the scope of the process within a mild and scalable protocol.

Introduction

In recent years, the use of synthetic organic photochemistry has increased significantly. Within an industrial setting, photochemical methods have historically employed UV radiation to directly excite organic molecules.[1] However, current research endeavors are focusing on harnessing visible light for synthetic applications, and these have started to become of interest industrially as a viable route to pharmaceutically active compounds.[2] With an increasing number of domestic light sources available (LED/CFL technologies), an array of synthetic methodologies utilizing visible light have been published and implemented in a variety of applications, with improved selectivity credited to the lower energy wavelengths used.[3] However, despite substantial advances, light sources used by synthetic organic chemists in photochemical transformations still remain poorly understood or not considered at all, with reaction conditions optimized to their light source at a single power setting. Internally it has been found that moving to a new light source on up-scaling often necessitates subsequent re-optimization.

The nature of the light source is central to the understanding of photochemical reactions. Light is an essential component in these transformations, yet sources used in synthetic applications are often poorly characterized broad-spectrum lamps.[4] Although this seemingly allows a convenient “one size fits all” solution, a more targeted approach is now possible with the development of pseudo-monochromatic light sources. This targeted approach allows for the in-depth development of a robust and fully optimized reaction protocol, particularly for the delivery of active pharmaceutical ingredients (APIs). Modern high power pseudo-monochromatic LEDs offer significant benefits over other commonly used industrial light sources, not only in their precise spectral output but also in their comparatively low operating temperature, which is a result of enhanced efficiency.[5] This delivers a marked improvement upon medium-pressure mercury lamps, for example, which have multiple discrete emittance bands between 200-500 nm, leading to unwanted photochemical reactions. In addition, these lamps typically operate between 600-800 °C,[6] meaning that temperature control is a significant challenge, with unwanted thermal side reactions often observed. The use of narrow band filters can restrict spectral output to the desired wavelength, but this can significantly reduce the transmittance, making the approach wasteful, particularly when considering the cooling required to remove excess heat from the lamp and/or the reaction.

Since its first report almost a century ago, the Wohl-Ziegler benzylic bromination has been regularly implemented in synthesis.[7] The majority of applications use radical initiators, such as peroxides[8] or azo compounds,[9] to mediate the homolysis of bromine.[10] However, light is a cheap and renewable alternative to traditional initiation approaches, delivering a safer and more sustainable transformation. Consequently, the photochemical Wohl-Ziegler reaction is well-precedented, with recent studies using a range of light sources.[11] Our experience with this reaction using medium-pressure mercury lamps, and the evaluation of batch-to-batch variability within domestic light sources, demonstrated a need for improved understanding of the light source. This has prompted us to undertake a detailed investigation into the effect of the character of the light source on the Wohl-Ziegler bromination. To our knowledge, no such study has previously been conducted, and this has resulted in the use of a wide range of conditions, including the unnecessary use of UV irradiation, or a combination of both a radical initiator and irradiation.[12]

Photochemical benzylic brominations have previously been demonstrated under continuous conditions,[13-14] indicating the

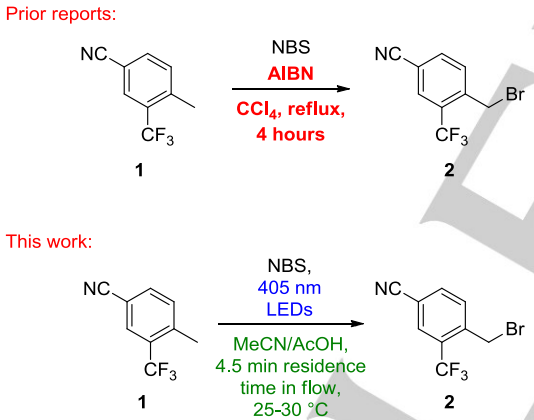
[a] H. E. Bonfield, W. X. Ooi, L. J. Edwards, Dr. J. D. Williams, Dr. S. G. Leach
API Chemistry, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (UK)
E-mail: lee.j.edwards@gsk.com
[b] Prof. Dr. W. J. Kerr, Dr. J. D. Williams
Department of Pure and Applied Chemistry
WestCHEM, University of Strathclyde
295 Cathedral Street, Glasgow, Scotland, G1 1XL (UK)
Email: w.kerr@strath.ac.uk

Supporting information for this article is given via a link at the end of the document.

potential scalability of this protocol, and thus its industrial applicability.[15] When considering the development of an industrial process, all reaction variables must be fully understood to ensure consistent product yield and quality, and in a photochemical reaction, irradiation character is no exception. In this respect, the light source should be optimized to the required wavelength and intensity, to minimize energy consumption and by-product formation.[16] Tuning the output of a light source can bestow further advantages, particularly by reducing the cooling requirement of the reaction system, which can present a challenge on larger scales.

Results and Discussion

As a model for our initial studies into the photochemical Wohl-Ziegler reaction, we selected 4-methyl-3-(trifluoromethyl)benzonitrile **1**, a challenging, electron-poor benzylic bromination substrate, which has been shown to require prolonged heating when using a chemically initiated protocol (**Scheme 1**).[17] Moreover, this substrate is of pharmaceutical interest making it an appropriate example to study in detail, enabling the factors which affect the reaction selectivity and productivity to be established.



Scheme 1. The benzylic bromination of **1**, studied in this report, under photochemical conditions.

In order to select the most suitable wavelength for irradiation, the reaction components were analyzed by UV-visible absorption spectroscopy in order to obtain confirmation of the photoactive species (**Figure 1**). Unsurprisingly, this revealed no absorbance above 350 nm for the reaction substrate **1**, *N*-bromosuccinimide (NBS), or a mixture of the two. However, the absorption spectrum of a sample of commercially obtained NBS, without prior purification, showed significant overlap with that of bromine (λ_{max} = 395 nm), indicating that low levels of bromine are responsible for the photochemical initiation of this benzylic bromination. The low Br-Br bond strength (190 kJ mol^{-1})[18] suggests that light with

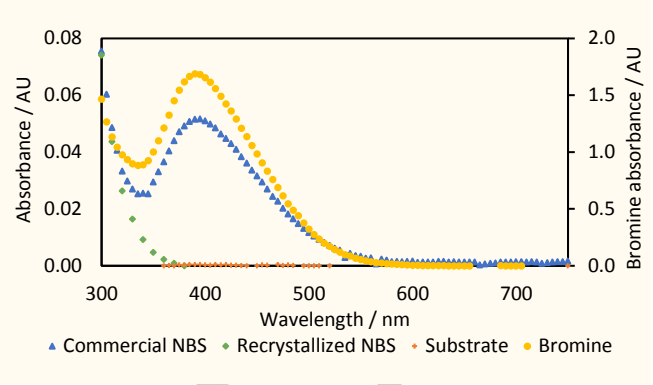
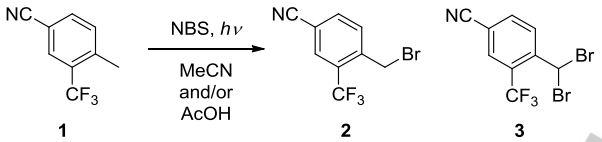


Figure 1. UV-visible absorption spectroscopy (300-750 nm) of the reaction components in the benzylic bromination of 4-methyl-3-(trifluoromethyl)benzonitrile (**1**).

a wavelength shorter than 630 nm is sufficiently energetic to promote homolysis. Accordingly, an LED which has a spectral output close to 395 nm should be most suitable in this reaction, leading to the use of visible light LEDs (λ > ~400 nm). Following on from these observations, it was realized that the quantity of bromine present in a sample of NBS can be determined in a straightforward manner using UV-visible absorption spectroscopy. Varying levels of bromine in NBS could impact the reaction rate and impurity profile, therefore an assay method to determine the bromine levels is desirable and, to our knowledge, has not been discussed in prior publications. Construction of an absorption calibration curve, using known concentrations of bromine, allowed the quantity of bromine in a commercial sample of NBS to be quantified as 3.1 mol%. This dropped to an undetectable level (< 0.1 mol%) following recrystallization from water, indicating that the remaining trace bromine is sufficient to initiate the reaction.

With this information in hand, investigation of reaction conditions was performed using high throughput screening (48-well plates), under irradiation by pseudo-monochromatic LEDs (**Table 1**). Initial screening reactions at a range of substrate and NBS concentrations in acetonitrile gave promising results, with up to 78% monobrominated product formation in one hour (entries 1-5). However, alongside the expected benzylic bromide product **2**, an appreciable level of the corresponding dibrominated compound, 4-(dibromomethyl)-3-(trifluoromethyl)benzonitrile **3** was observed, presumably due to the poor energetic differentiation between H-atom abstraction from the starting material **1** and the desired product **2**.[19] Furthermore, this second bromination led to consumption of additional NBS, such that unreacted starting material **1** also remained. It is hypothesized that bromine formation from NBS is favoured under Brønsted acidic conditions,[20] allowing the concentration of bromine radical sufficient for reaction to be reached more quickly. The addition of acetic acid (entry 6 versus entry 8) enhanced the rate of reaction significantly, allowing near-complete conversion in just five minutes, while extending the reaction time to 60 min under these conditions offering no significant benefit (entry 7). Increasing the number of NBS equivalents to 1.5 (entry 8 versus entry 9) showed similar reaction composition at five minutes but also



1 2 3

Table 1. Reaction optimization: varying concentration, NBS loading and solvent composition.[a]

Entry	Solvent	Time (min)	Conc. (M)	NBS loading (eq.)	Remaining 1 (%)[b]	2 (%)[b]	3 (%)[b]
1	MeCN	60	0.1	1.05	12	66	1
2	MeCN	60	0.2	1.05	14	70	2
3	MeCN	60	0.3	1.05	11	74	2
4	MeCN	60	0.4	1.05	13	74	3
5	MeCN	60	0.5	1.05	9	78	4
6	MeCN	5	0.3	1.05	80	17	0
7	MeCN/AcOH (1:1)	60	0.3	1.05	5	78	5
8	MeCN/AcOH (1:1)	5	0.3	1.05	12	77	4
9	MeCN/AcOH (1:1)	5	0.3	1.5	7	80	7
10	MeCN/AcOH (1:1)	60	0.3	1.5	0	54	29
11	MeCN/AcOH (1:1)	5	0.1	1.5	5	75	5
12	MeCN/AcOH (99:1)	5	0.1	1.5	81	17	0
13	MeCN/AcOH (8:2)	5	0.1	1.5	42	52	1
14	AcOH	5	0.1	1.5	2	70	19
15[c]	MeCN/AcOH (1:1)	5	0.1	1.5	5	79	8
16[d]	MeCN/AcOH (1:1)	5	0.1	1.5	9	76	4

[a] Light source was set to 200 mA current. [b] Quoted yields are HPLC %area. [c] Reaction performed using 420 nm LEDs set to 200 mA current. [d] Reaction performed using 450 nm LEDs set to 200 mA current.

overbromination to by-product **3** over time (entry 9 versus entry 10). Investigation of acetic acid loading (entries 11 to 14) indicated that either increasing or decreasing the quantity of acetic acid from a 1:1 ratio with MeCN causes deviation from the optimal yield of product **2**. When varying the wavelength of the light source (405 nm in entries 1-14, 420 nm in entry 15, and 450 nm in entry 16), a similar final reaction composition was observed. However, upon more detailed examination, the 405 nm light source was found to mediate the transformation at a faster rate, so its use was continued throughout the remainder of this investigation.[21]

Additional control reactions were performed, which confirmed that no reaction occurred in the absence of light, or in the presence of a radical inhibitor species.[22] Importantly, it was also observed that continual irradiation of the reaction mixture was required, as no further reaction was observed following removal of the light source, prior to reaction completion. This implies that radical chain propagation processes alone are not sufficient to sustain the reaction, and continued energy input from an external source is necessary.

Further understanding of the course of reaction was sought through more in-depth reaction profiling. This was used to compare the rate of starting material **1** consumption (**Figure 2a**), alongside formation of product **2** and by-product **3**, under irradiation at different light intensities. These varied intensities were accessed using tunable 405 nm LEDs, whose input power was found to have a linear relationship with output intensity, as measured in lux (**Figure 2b**). As light intensity was decreased, a more pronounced initiation period was observed prior to reaction progression. This was most notable in the reaction run using 30 mA current (giving the lowest possible output power), which appeared to have an initiation period of approximately 2 minutes. Initiation periods have been studied previously in halogenation reactions which use a radical initiator [23] but, to our knowledge, never within the photochemically-initiated variant. Substantially shorter initiation periods were exhibited at higher light intensities, until no significant rate difference was observed, between 200 mA, 300 mA and 400 mA currents [24]. This implies that the reaction mixture is light-saturated at these higher light intensities, and the reaction is therefore operating within an entirely reagent-limited

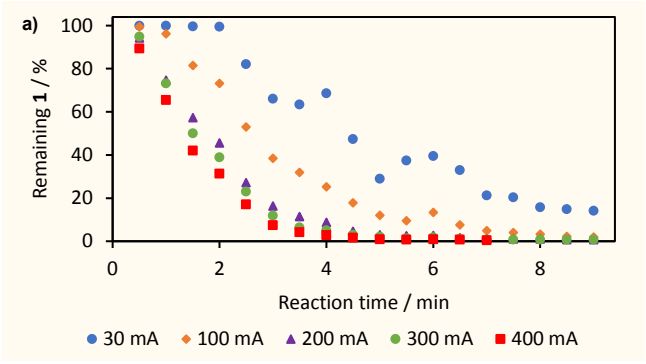


Figure 2. a) The effect of light intensity upon rate of reaction showing starting material consumption over time, for the benzylic bromination of **1** at different light intensities. b) Calibration of luminous flux with changing current.

kinetic regime. This can be explained by the relatively low concentration of bromine present in these reactions, which allows substantially higher light transmission than in many other photochemical reactions. 200 mA current was chosen for all further reactions, based on this observation.

The influence of bromine content on the length of initiation period was demonstrated by comparison of time courses between recrystallized and commercial NBS (**Figure 3**). Upon exclusion of bromine, a more distinct initiation period was observed, with a peak quantity of product **2** observed after 5.5 minutes, compared to 4.5 minutes. However, both reactions displayed the same reaction composition at peak conversion, with 3-5% remaining starting material **1**, 77-78% desired product **2** and 8% of the unwanted overbrominated by-product **3**. Since the commercial NBS reached peak conversion slightly faster, it was used in all other reactions.

The optimal reaction conditions (using 405 nm LEDs, at 200 mA current (40% of the maximum light intensity)) were applied to the reaction in flow, where the residence time was optimized to achieve maximum conversion to monobrominated product **2**, whilst minimizing the time allowed for formation of dibrominated by-product **3**. From the 5 minute reaction time required in batch (**Table 1**, entry 9), the optimal residence time was decreased to 2.5 minutes (**Figure 4a**), due to the improved light penetration and mixing achieved when using a highly turbulent microreactor (4.09 mL volume) in flow.[25-26] Upon reducing the number of NBS equivalents to 1.05, a longer residence time of 5 minutes (**Figure 4b**) was required to maintain an excellent yield of the desired product **2**. Under these conditions, one gram of material was processed, with a consistent reaction profile over the 20 minute run duration, leading to a 69%

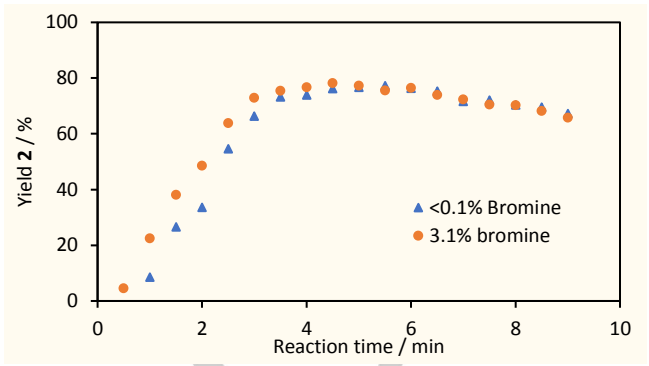


Figure 3. Comparative reaction profile of two NBS samples, containing different levels of bromine, as determined by UV-visible absorption spectroscopy.[27]

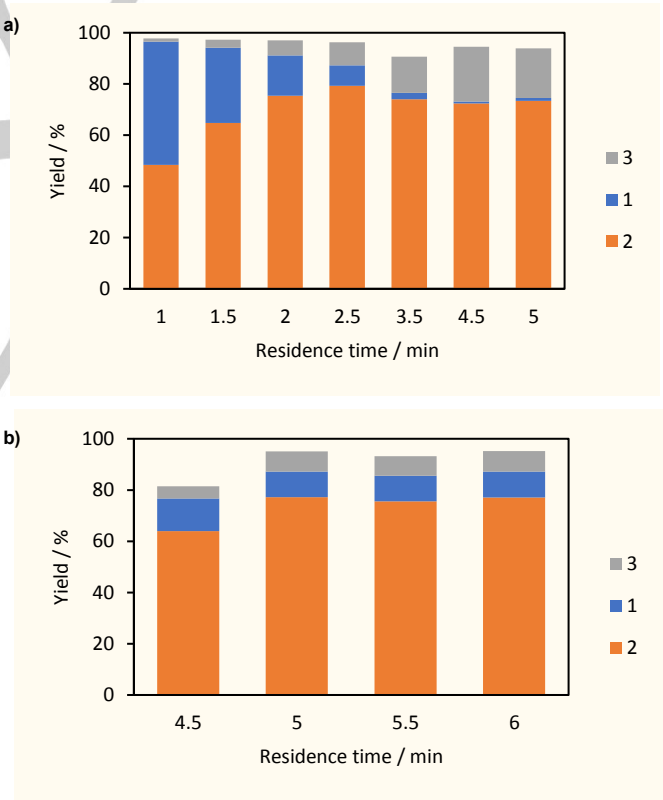
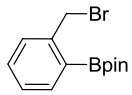
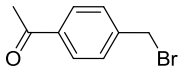
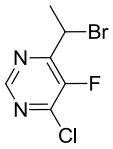
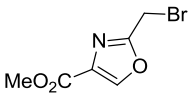
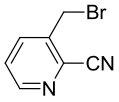
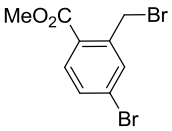
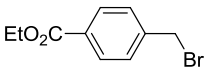
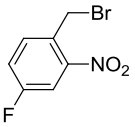
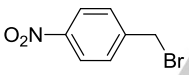


Figure 4. Product distribution of benzylic bromination of **1** in flow, using different residence times, to determine the optimal flow rate. λ = 405 nm, current = 200 mA. a) Flow rate optimization using 1.5 eq. NBS, displaying an optimal product **2** yield at 2.5 minute residence time. b) Flow rate optimization using 1.05 eq. NBS, displaying an optimal product **2** yield at 5 minute residence time.

Table 2. Substrate scope examined under flow conditions. λ = 405 nm, 200 mA current. 1 mmol of substrate was processed.

Entry	Product	Compound	NBS loading (eq.)	Residence time (min)	Conversion (%)[a]	Product yield (%)[b][c]
1		**4**	1.05	2.0	100	94 (80)
2		**5**	1.05	1.36	95	83 (53)
3		**6**	1.05	1.36	97	87 (35)
4		**7**	1.5	18	82	57 (43)
5		**8**	1.5	9	87	69 (49)
6		**9**	1.05	1.36	98	91 (89)
7		**10**	1.05	1.36	94	85 (30)
8		**11**	1.5	4.54	96	74 (53)
9		**12**	1.5	1.36	91	80 (47)

[a] Conversion based on percentage of starting material consumed by HPLC %area. [b] Yield of the desired product, as determined by HPLC %area. [c] Isolated yield of the desired product is shown in parentheses.

isolated yield of the monobrominated product **2**.

The procedure was then applied to the benzylic bromination of a range of electron-deficient aromatic and heteroaromatic compounds (**Table 2**). NBS equivalents and residence times for each substrate were selected based on an initial substrate screen, [28] and no further optimization was performed. In flow all substrates underwent facile conversion to their corresponding benzylic bromides within very short residence times. The presence of a boronic ester (entry 1) was well tolerated, providing the desired product **4** in a residence time of just 2 minutes. Selective formation of product **5** was achieved (entry 2), and no α-bromination of the ketone was observed. This has been known to occur in the presence of elemental bromine under acidic conditions.[29] A heavily functionalized pyrimidine core was brominated on its ethyl group (entry 3) in just 1.36 minutes, whereas two other heterocyclic cores (entries 4 and 5) required extended residence times (18 and 9 minutes, respectively) and a higher NBS loading, in order to achieve good conversion. Ester-containing aromatics (entries 6 and 7) were brominated smoothly, yet those furnished with a nitro group (entries 8 and 9) required

an increased NBS loading. Notably, excellent temperature control was maintained throughout these reactions, typically keeping the flow plate temperature below 30 °C, with the exception of the examples using slower flow rates (entry 4 reached a maximum temperature of 60 °C and entry 5 reached 40 °C).[30] It is possible that in these examples, the higher temperature may have resulted in poorer selectivity for the desired monobrominated products.

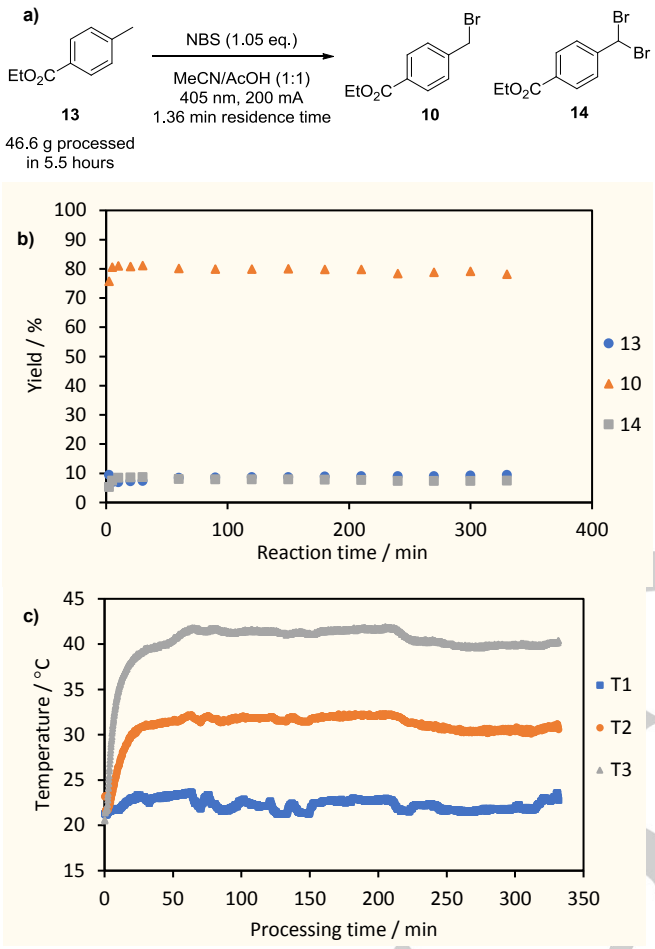


Figure 5. a) Reaction scheme for the large scale bromination of ester **13**, to form its benzylic bromide, **10**. **b)** Chart showing the reaction profile throughout the 5.5 hour operating time. Reaction yields are measured by HPLC, using %Area values. **c)** Reaction temperature profile throughout the 5.5 hour operating time. T1 = input temperature, T2 = output temperature, T3 = reactor temperature.

The flow protocol was examined on a larger scale, by running the reaction continuously for 5.5 hours (**Figure 5a**). Due to the fast reaction rates of the protocol, this elongated run encompassed 243 residence times, within which 46.6 g of starting material was processed. The reaction composition (**Figure 5b**) was monitored throughout, displaying a steady profile after the initial equilibration period. During this period the reaction temperature was also measured at the reactor entrance and exit, and within the reactor itself, in order to accurately illustrate the temperature profile (**Figure 5c**).[31] The reactor temperature (T3) was found to reach steady state between 40-42 °C, and maintained this throughout the run. This larger scale reaction demonstrates the industrial applicability of the developed procedure, by exemplifying consistent reaction profile and temperature control within a continuous flow process. The desired product **10** was then isolated via an unoptimized recrystallization in 40% yield (27.5 g), comparable to the smaller scale reaction (**Table 2**, entry 7). It was subsequently found that **10** could be generated in a solution yield of 58% at 400 mA current, using a significantly shorter 0.20 minute residence time. This compares favourably with the 57% solution yield achieved using 200 mA current with a 1.36 minute residence time, as throughput is increased 6-fold.[32]

Finally, our optimization methodology was applied to **15** (**Table 2**, entry 6) to identify the optimal intensity and flow rate for the generation of **9** in higher throughput. Different light intensities and flow rates were screened (**Figure 6b**). It was found that 350 mA current allowed a flow rate of 10 mL/min (0.41 minute residence time). These conditions were advantageous when compared to those from the original optimization (200 mA current, 3 mL/min flow rate 1.36 minute residence time), and thus were used to process 30 g of **15**. An additional 5 g of **15** were processed using the lower light intensity and longer residence time. The reaction profiles for both sets of conditions were similar by HPLC[33] and isolated yields of 62% (25 g, with mother liquors containing a further 2.5% (1.07 g)) and 71% (4.8 g, with mother liquors containing a further 18% (1.22 g)) were achieved respectively, via an unoptimized recrystallization. These yields are consistent with the solution yields realized in **Figure 6b**.

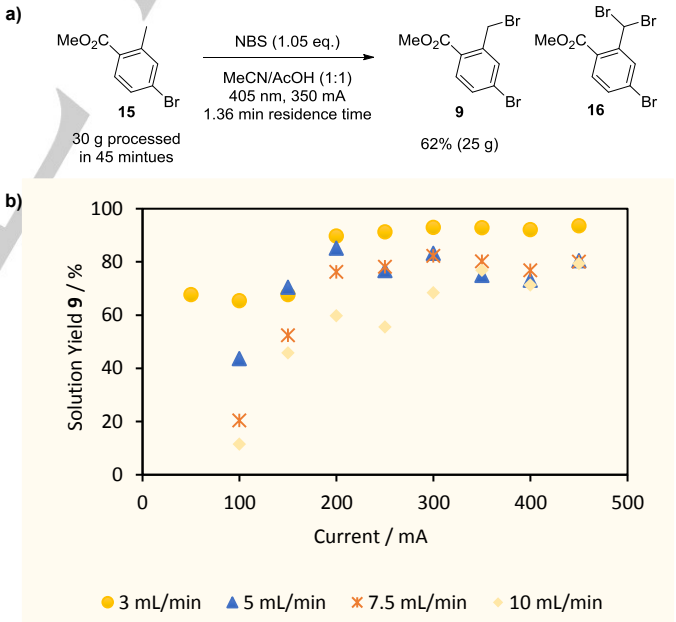


Figure 6. a) Reaction scheme for the large scale bromination of ester **15**, to form its benzylic bromide **9**. **b)** Chart showing the solution yield of reaction at different flow rates and light intensities.

Conclusions

Our studies have shown that pseudo-monochromatic visible light LEDs provide effective irradiation for the photochemical

Wohl-Ziegler benzylic bromination using NBS. By using a platform capable of varying light intensity, it has been possible to develop a protocol that uses only a fraction of the maximum LED power, thereby developing our understanding of power and cooling requirements, when scaling photochemical processes from the lab to an industrial platform.

Scaling up of this process was demonstrated from screening through to running the reaction continuously for 5.5 hours in flow with the same pseudo-monochromatic light source. Consequently, reliable temperature control has been achieved in flow, for a reproducible reaction, with minimal energy wastage. We have also applied this methodology to a range of other substrates, where excellent conversions were achieved with a residence time of less than 2 minutes in many cases.

We have demonstrated how our strategy of optimizing the light source to suit the required chemical transformation can be applied. In doing so we have developed generic conditions for the exemplar substrate that can be applied to other substrates and methodology that can be applied to further optimize each substrates, either for quality or throughput. We anticipate that an improved emphasis on the nature and power of light source used, particularly by synthetic organic chemists, will allow development of more efficient and selective photochemical processes which are directly transferrable to industry.

Experimental Section

Detailed experimental procedures for all experiments, and characterization data for all products are available in the supporting information.

General batch protocol: 1 mL of a 0.1 M solution containing 4-methyl-3-(trifluoromethyl)benzonitrile (1 eq.) and *N*-bromosuccinimide (1.5 eq.) in 1:1 MeCN:AcOH was charged to 48 × 2 mL vials and each inserted into a 48-well plate on the photoreactor. The vials were irradiated at a chosen wavelength and light intensity, for the desired length of time. Time course experiments were performed by removing a reaction vial every 30 seconds, for HPLC analysis.

General flow protocol: A 0.3 M solution of bromination substrate and *N*-bromosuccinimide (1.05 - 1.5 eq.) in 1:1 MeCN:AcOH was irradiated with an array of 48 × LEDs (405 nm wavelength, set to 200 mA input current), whilst being passed through a glass plate flow reactor at an optimized flow rate. After the required volume of reaction mixture had entered the reactor, the reaction mixture was collected for a time equivalent to four reactor volumes. The desired product was isolated as specified in each individual example.

Acknowledgements

The authors thank Mr Peter Gray and Mr Khushaal Sharma for their aid in developing the photoreactor, Dr. David M. Lindsay for assistance in manuscript preparation, Mr. Thomas Atherton for mass spectrometry support and Mr Graham Rutherford for HiTec Zang programming support. J.D.W. would also like to thank GlaxoSmithKline for financial support.

Keywords: Flow Chemistry • Halogenation • Microreactors • Photochemistry • Reaction mechanisms

[1] Reviews of direct excitation UV photochemistry in organic synthesis: a) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052–1103; b) B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558–7564; c) J. D. Winkler, C. M. Bowen, F. Liotta, *Chem. Rev.* **1995**, *95*, 2003–2020; d) M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453–1473.

[2] Selected examples of photochemical processes in drug discovery and development: a) J. J. Douglas, M. J. Sevrin, C. R. J. Stephenson, *Org. Process Res. Dev.* **2016**, *20*, 1134–1147; b) M. Fischer, *Angew. Chem.* **1978**, *90*, 17–27; M. Fischer, *Angew. Chem. Int. Ed.* **1978**, *17*, 16–26; c) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276–10341; d) Z. Amara, J. F. B. Bellamy, R. Horvath, S. J. Miller, A. Beeby, A. Burgard, K. Rossen, M. Poliakoff, M. W. George, *Nat. Chem.* **2015**, *7*, 489–495; e) J. Turconi, F. Griolet, R. Guevel, G. Oddon, R. Villa, A. Geatti, M. Hvala, K. Rossen, R. Göller, A. Burgard, *Org. Process Res. Dev.* **2014**, *18*, 417–422.

[3] Reviews of visible light photochemistry in organic synthesis: a) C. K. Prier, D. A. Rankic, D. W. C. Macmillan, *Chem. Rev.* **2013**, *113*, 5322–5363; b) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387–2403; c) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Soc. Rev.* **2016**, *45*, 2044–2056; d) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926.

[4] Selected examples of synthetic chemistry using broad spectrum light sources: a) A. Yavorskyy, O. Shvydkiv, N. Hoffmann, K. Nolan, M. Oelgemöller, *Org. Lett.* **2012**, *14*, 4342–4345; b) Y. S. M. Vaske, M. E. Mahoney, J. P. Konopelski, D. L. Rogow, W. J. McDonald, *J. Am. Chem. Soc.* **2010**, *132*, 11379–11385; c) D. C. Harrowven, M. Mohamed, T. P. Gonçalves, R. J. Whitby, D. Bolien, H. F. Sneddon, *Angew. Chem.* **2012**, *124*, 4481–448; D. C. Harrowven, M. Mohamed, T. P. Gonçalves, R. J. Whitby, D. Bolien, H. F. Sneddon, *Angew. Chem. Int. Ed.* **2012**, *51*, 4405–4408; d) J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem.* **2014**, *126*, 512–516; J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502–506; e) L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607–5610.

[5] a) C. Le, M. K. Wismer, Z.-C. Shi, R. Zhang, D. V. Conway, G. Li, P. Vachal, I. W. Davies, D. W. C. MacMillan, *ACS Cent. Sci.* **2017**, *3*, 647–653; b) Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, *20*, 10562–10589; c) D. H. Chen, X. Ye, K. Li, *Chem. Eng. Technol.* **2005**, *28*, 95–97.

[6] J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.

[7] Seminal publication, and reviews of the Wohl-Ziegler reaction: a) A. Wohl, *Berichte der Deutschen Chemischen Gesellschaft* **1919**, *52*, 51–63; b) C. Djerassi, *Chem. Rev.* **1948**, *43*, 271–317; c) I. Saikia, A. J. Borah, P. Phukan, *Chem. Rev.* **2016**, *116*, 6837–7042.

[8] Selected recent examples: a) J. Emmerich, C. J. Van Koppen, J. L. Burkhart, Q. Hu, L. Siebenbürger, C. Boerger, C. Scheuer, M. W. Laschke, M. D. Menger, R. W. Hartmann, *J. Med. Chem.* **2017**, *60*, 5086–5098; b) C. J. Evoniuk, G. D. P. Gomes, S. P. Hill, S. Fujita, K. Hanson, I. V. Alabugin, *J. Am. Chem. Soc.* **2017**, *139*, 16210–16221; c) C. Chen, X. Chen, X. Zhang, S. Wang, W. Rao, P. W. H. Chan, *Adv. Synth. Catal.* **2017**, *359*, 4359–4368.

[9] Selected recent examples: a) D. Feng, J. Wan, F. Teng, X. Ma, *Catal. Commun.* **2017**, *100*, 127–133; b) W. Xun, B. Xu, B. Chen, S. Meng, A. S. C. Chan, F. G. Qiu, J. Zhao, *Org. Lett.* **2018**, *20*, 590–593; c) H. Shimojo, K. Moriyama, H. Togo, *Synthesis* **2015**, *47*, 1280–1290; d) M. Bersellini, G. Roelfes, *Org. Biomol. Chem.* **2017**, *15*, 3069–3073; e) S. Lee, O. S. Kwon, C. S. Lee, M. Won, H. S. Ban, C. S. Ra, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3026–3029; f) Y. Chen, Y. Liu, Y. Yao, S. Zhang,

Z. Gu, Q. Jin, J. Ji, X. He, K. Wang, *Org. Biomol. Chem.* **2017**, *15*, 3232–3238.

[10] G. A. Russell, C. DeBoer, K. M. Desmond, *J. Am. Chem. Soc.* **1963**, *85*, 365–366.

[11] a) A. Podgoršek, S. Stavber, M. Zupan, J. Iskra, *Tetrahedron Lett.* **2006**, *47*, 1097–1099; b) C. H. M. Amijs, G. P. M. van Klink, G. van Koten, *Green Chem.* **2003**, *5*, 470–474.

[12] a) M. Giroud, J. Ivkovic, M. Martignoni, M. Fleuti, N. Trapp, W. Haap, A. Kuglstatter, J. Benz, B. Kuhn, T. Schirmeister, F. Diederich, *ChemMedChem* **2017**, *12*, 257–270; b) Y. Wang, H. Fan, K. Balakrishnan, Z. Lin, S. Cao, W. Chen, Y. Fan, Q. A. Guthrie, H. Sun, K. A. Teske, V. Gandhi, L. A. Arnold, X. Peng, *Eur. J. Med. Chem.* **2017**, *133*, 197–207; c) T. V Shishkanova, M. Havlík, M. Dendisová, P. Matějka, V. Král, *Chem. Commun.* **2016**, *52*, 11991–11994.

[13] Photochemical benzylic bromination in flow using molecular bromine: Y. Manabe, Y. Kitawaki, M. Nagasaki, K. Fukase, H. Matsubara, Y. Hino, T. Fukuyama, I. Ryu, *Chem. Eur. J.* **2014**, *20*, 12750–12753.

[14] Photochemical benzylic bromination in flow using NBS: a) D. Cantillo, O. de Frutos, J. A. Rincon, C. Mateos, C. Oliver Kappe, *J. Org. Chem.* **2014**, *79*, 223–229; b) D. Šterk, M. Jukič, Z. Časar, *Org. Process Res. Dev.* **2013**, *17*, 145–151.

[15] Reviews highlighting the applicability of flow chemistry to industrial processes: a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem.* **2015**, *127*, 6788–6832; B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2–25; c) D. L. Hughes, *Org. Process Res. Dev.* **2018**, *22*, 13–20.

[16] Energy efficiency in relation to the Twelve Principles of Green Chemistry: P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312.

[17] Synthesis of this compound by benzylic bromination: a) A. Quattropani, W. H. B. Sauer, S. Crosignani, J. Dorbais, P. Gerber, J. Gonzalez, D. Marin, M. Muzerelle, F. Beltran, A. Nichols, K. Georgi, M. Schneider, P-A. Vitte, V. Eligert, L. Novo-Perez, J. Hantson, S. Nock, S. Carboni, A. L. S. de Souza, J-F. Arrighi, U. Boschert, A. Bombrun, *ChemMedChem* **2015**, *10*, 688–714; b) G. M. Ksander, E. Meredith, L. G. Monovich, J. Papillion, F. Firooznia, Q-Y Hu, Condensed Imidazolo Derivatives for the Inhibition of Aldosterone Synthase and Aromatase, **2007**, WO 2007/024945 A1; c) Y. Ding, R. K. Thalji, J. P. Marino, Novel SHE Inhibitors and their Use, **2009**, WO 2009/049165 A1; d) J. E. Hunter, W. C. Lo, G. B. Watson, A. Patny, G. D. Gustafson, D. Pernich, W. K. Brewster, D. L. Camper, B. Lorsbach, M. R. Loso, T. C. Sparks, H. Joshi, A. Mandaleswaran, R. Sanam, R. Gundla, P. S. Iyer, Pesticidal Compositions and Process Related Thereto, **2012**, WO 2012/177813 A1; e) W. C. Lo, J. E. Hunter, G. B. Watson, A. Patny, P. S. Iyer, J. Boruwa, Pesticidal Compositions and Process Related Thereto, **2014**, US 2014/0171314 A1.

[18] B. de B. Darwent in *National Standard Reference Data Series, No. 31,* National Bureau Of Standards, Washington, DC, **1970**.

[19] DFT calculations (UB3LYP/6-311G++(d,p)) found the barrier for hydrogen atom abstraction from the benzylic position of **1** and **2** to be +6.0 kcal mol^{-1} and +9.1 kcal mol^{-1}, respectively. Although there is a significant difference between the two, both barriers are sufficiently low to allow the process to occur in a facile manner at room temperature, hence both are likely to be indistinguishable. See supporting information for details.

[20] W. Offermann, F. Vögtle, *Synthesis* **1977**, 272–273.

[21] See supporting information (Figure S25) for more detailed reaction profile comparing different LED wavelengths.

[22] See supporting information for details of control reactions demonstrating: no reaction in the dark, or in the presence of TEMPO, and reaction ceasing upon removal of light source.

[23] P. Goldfinger, P. A. Gosselain, R. H. Martin, *Nature* **1951**, *168*, 30–32.

[24] See the supporting information (Figure S24) for time courses of benzylic bromination of the model substrate with *N*-bromosuccinimide at 405 nm from 30 to 400mA.

[25] Examples highlighting improved reaction performance in flow, particularly using a microreactor: a) E. E. Coyle, M. Oelgemöller, *Photochem. Photobiol. Sci.* **2008**, *7*, 1313; b) K. Loubière, M. Oelgemöller, T. Aillet, O. Dechy-Cabaret, L. Prat, *Chem. Eng. Process.* **2016**, *104*, 120–132; c) L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Erlebe, M. B. Berry, K. I. Booker-Milburn, *Chem. Eur. J.* **2014**, *20*, 15226–15232; d) K. Pimparkar, B. Yen, J. R. Goodell, V. I. Martin, W.-H. Lee, J. A. Porco, A. B. Beeler, K. F. Jensen, *J. Flow Chem.* **2011**, *1*, 53–55.

[26] See the supporting information for experimental characterization of the flow reactor used in this study.

[27] See the supporting information for details of the method used (General method A).

[28] See the supporting information for details of initial substrate screening in batch.

[29] Synthesis and characterization data for 2-bromo-1-(4-methylphenyl)ethanone: a) T. Ganesh, C.H. Kumar, G. L. D. Krupadanam, *Synth. Commun.* **1999**, *29*, 2069-2078; b) B. Rammurthy, P. Swamy, M. Naresh, C. Durgaiah, G. K. Sai, N. Narender, *New J. Chem.* **2017**, *41*, 3710-3714.

[30] See the supporting information for a temperature profile of each reaction.

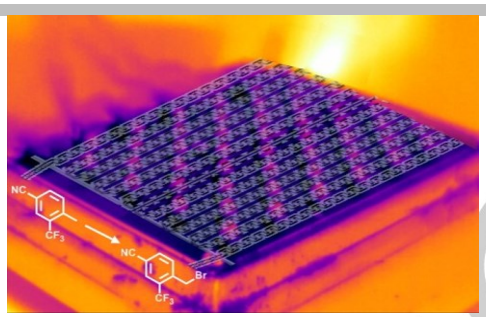
[31] See the supporting information for an engineering line diagram (ELD) of the flow reaction setup, denoting the placement of all three temperature probes.

[32] See the supporting information *(*Figure S41*)* for details of light intensity and flow rate optimization for the bromination of **13**.

[33] See the supporting information (Figure S54 and S56) for HPLC reaction profiles throughout both reactions.

ARTICLE

And then there was light: The significance of defining light power requirements within photochemical reactions has been exemplified using the Wohl-Ziegler reaction in batch and flow.



*Holly E. Bonfield, Jason D. Williams, Wei Xiang Ooi, Stuart G. Leach, William J. Kerr and Lee J. Edwards**

Page No. – Page No.

A Detailed Study of Irradiation Requirements, Towards an Efficient Photochemical Wohl-Ziegler Protocol in Flow