Organic & Biomolecular Chemistry

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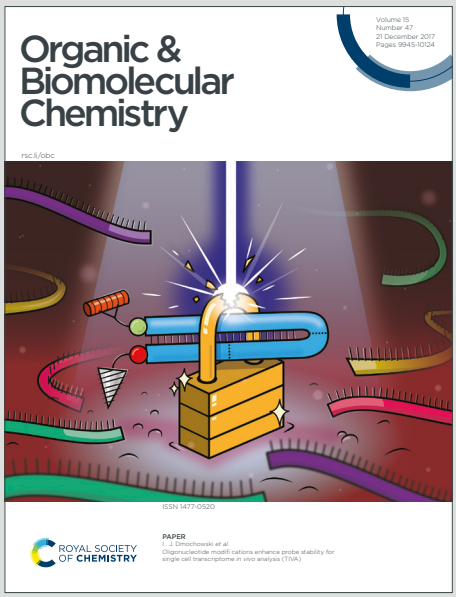

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DOI: 10.1039/D0OB00821D

ARTICLE

The Breaking Beads Approach for Photocleavage from Solid Support

Yasmeen Bakhatan[a], Israel Alshanski[a], Dana Grunhaus[a] and Mattan Hurevich[a]*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Photocleavage from polystyrene beads is a pivotal reaction for solid phase synthesis that relies on photolabile linkers. Photocleavage from intact porous polystyrene beads is not optimal because light cannot penetrate into the beads and the surface area exposed to irradiation is limited. Thus, hazardous, technically challenging and expensive setups are used for photocleavage from intact beads. We developed a new concept in which grinding the beads during or prior to irradiation is employed as an essential part of the photocleavage process. By grinding the beads we are exposing more surface area to the light source, hence, photocleavage can be performed even using a simple benchtop LED setup. This approach proved very efficient for photocleavage of various model compounds including fully protected oligosaccharides.

Introduction

Photolabile groups provide an additional level of orthogonality to other common protecting groups.[1-3] They are used as handles to connect solid support to a synthesized molecule in solid phase synthesis (SPS).[4] These linkers are very attractive for SPS because they are stable to many reaction conditions and can be liberated under very mild conditions.[5-16] Photolabile linkers are especially valuable for oligosaccharide and glycoconjugate synthesis because they proved to be orthogonal and stable to the multiple synthetic manipulations required.[17-23] Photochemical reactions on the solid support are not as straightforward as in a solution. Polystyrene beads are insoluble, not transparent and porous. The efficiency of irradiation depends on the ability of the light not only to cover the entire surface of the beads but also to penetrate into the pores that contain the synthesized molecules anchored to photolabile linkers. Therefore, batch irradiation of solid support tends to suffer from heterogeneity problems, and photocleavage is inefficient.[24] Irradiation by mercury lamp in continuous flow reactors provides more efficient photocleavage because the beads are exposed to the light for a longer time and from a close distance.[25-27] Flow-based irradiation reactor is a technical improvement that contributed dramatically to expedite automated synthesis of even extremely large oligosaccharides and made photolabile linkers the preferred choice for these transformations.[28-30] However, the irradiation of solid material in flow is still very challenging. First, many reactors rely on the use of mercury lamps which is hazardous. Second, light-emitting diode LED in flow reactor is becoming more common, which is safer, demands the assembly of complicated home-made setups or the purchasing of commercially available and expensive ones. Third, there is always a risk of insufficient spacing between beads which can hamper the efficiency of cleavage. Fourth, flow reactors cannot be paused during irradiation to check for progress.[6, 14-16] It is difficult to reach high cleavage efficiency even in flow probably because light cannot penetrate the inner part of the beads.[24] As a common solid phase practice, the integrity of the beads is preserved in these photocleavage processes.[31] We figured that since the photocleavage is the last step performed on the solid support, the integrity of the beads is not important anymore. A recent report suggested that after stirring polystyrene beads with a magnetic bar, the ground beads are much smaller than the original mesh size but are still big enough to be separated from the cleaved product by simple filtration of the solution.[32, 33] We assumed that grinding the beads during the irradiation will increase the surface area exposed to light and might improve cleavage efficiency while it will not hamper the simple filtration separation process. Here, we present a simple benchtop light-emitting diode (LED) batch system for photocleavage from the solid support. The system takes advantage of magnetic stirring to grind the beads during or before irradiation in to expose more surface area to the light source. We evaluated the effect of stirring and the size of the beads on the irradiation efficiency and on the ability to cleave protected oligosaccharides.

Results and Discussion

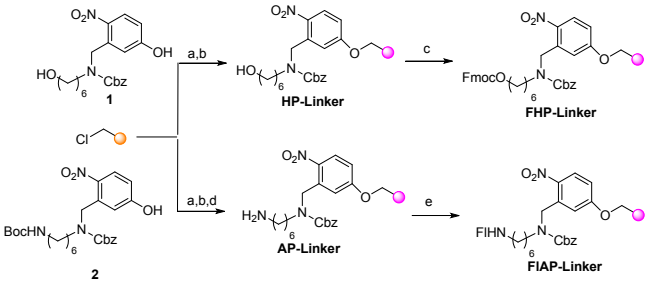
Preparation and labelling of photolabile linkers.

Two different photocleavage handles **1** and **2** were prepared in a solution following previously reported procedure.[20, 25, 26] A

[a] *Department: The institute of chemistry and The Harvey M. Kreuger Family Center for Nanoscience and Nanotechnology*
Institution: The Hebrew University of Jerusalem.
Address: Jerusalem, 91904, Israel.
E-mail: mattan.hurevich@mail.huji.ac.il

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Merrifield resin was treated with **1** under basic conditions to provide hydroxyl functionalized photolabile linker **HP-Linker** (Scheme 1). The **HP-Linker** was reacted with Fmoc-Cl to provide **FHP-Linker** that can be used for loading quantification and cleavage efficiency evaluation. Similarly, Merrifield resin was treated with **2** to provide amine functionalized photolabile linker **AP-Linker**. The amine of **AP-Linker** was reacted with fluorescein to provide the fluorescent photolabile linker **FlAP-Linker** for the evaluation of cleavage efficiency by fluorescent microscopy.



Scheme 1. Synthesis and labelling of amino and hydroxyl photolinkers. Reagents and conditions: a) DMF/DCM, $CsCO_3$, TBAI, 24 h, 60 °C, 870 mbar. b) CsOAc, DMF, 24 h, 60°C, 870 mbar. c) Fmoc-Cl, piperidine/DCM. d) 10 % TFA/DCM, twice 10 min. e) DMF/DCM, DIPEA, DIC, HOBt, fluorescein, 24 h.

Photocleavage setup and cleavage procedure.

In our irradiation setup, 25-100 mg of solid support was inserted into a quartz cuvette with a magnetic bar and 2 ml of dichloromethane (DCM) were added. This cuvette was placed on a stirring plate (Figure 1A). A high Power 365 nm LED lamp was positioned in a 2 cm distance from the cuvette and the entire setup was covered prior to commencing irradiation (Figure 1A). After irradiation, the beads were transferred and collected in a fritted filter Sep-Pak. The cleavage efficiency was determined either by the Fmoc quantification of the remaining uncleaved product (**FHP-Linker**) or by fluorescent microscopy (**FlAP-Linker**) (Figure 1). The DCM filtrate from the initial washing was used to quantify the amount of linker that was cleaved by irradiation as will be demonstrated later.

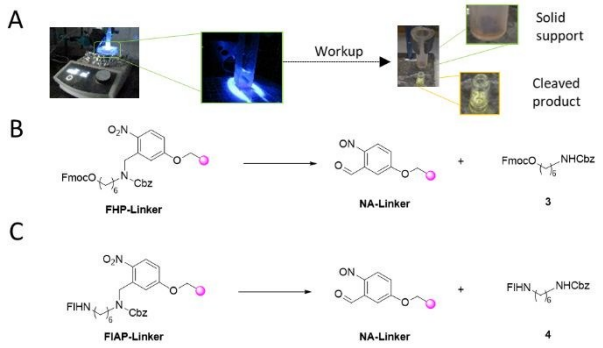


Figure 1. A) LED based photocleavage irradiation setup with stirring. After irradiation, the product was separated from the solid support by a simple filtration. B) Photo cleavage of **FHP-linker** to give **NA-linker** and *N*-Cbz-*O*-Fmoc-hexanolamine, **3**. C) Photo cleavage of **FIAP-linker** to give **NA-linker** and *N*-Cbz-*N*-fluorescein-hexanediamine **4.**

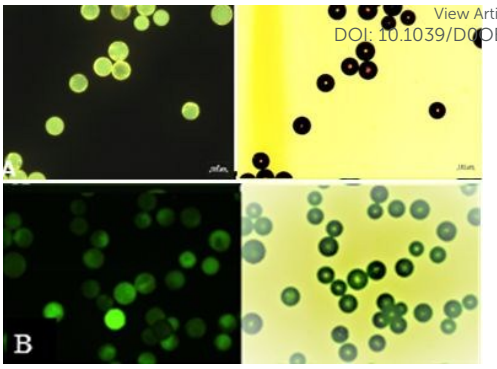


Figure 2. Irradiation without stirring resulted in incomplete cleavage. A) Fluorescent (left) and regular microscopy images (right) of **FlAP-Linker** before irradiation. B) Fluorescent (left) and regular microscopy images (right) of **FlAP-Linker** after irradiation for four hours of irradiation without stirring.

The inefficiency of Irradiation of the photolinker without stirring.

FlAP-Linker was irradiated for 2-8 hours in the LED setup without stirring (Figure 2 and SI). Fluorescent microscopy images of the beads were taken after each irradiation experiment and the mean fluorescence intensity was calculated and compared to the beads before irradiation (SI). The fluorescence intensity of the beads decreased as a factor of irradiation time showing that *N*-Cbz-*N*-fluorescein-hexanediamine **4** was cleaved from the solid support. After four hours of irradiation, there was still a significant fluorescence signal of the beads (Figure 2B). Full cleavage was not observed even after eight hours of irradiation. The images also showed that the integrity of the beads is preserved during irradiation without stirring. This suggests that either the mixing inefficiency hampered the exposure of the beads to light or/and that the ability of UV irradiation to penetrate the beads is limited. To overcome this potential limitation, we assumed that magnetic stirring, which increases the mixing efficiency and grinds the beads, can enhance the exposure to the light source and improve the photo-cleavage efficiency.[33]

The effect of magnetic stirring rate on photocleavage efficiency.

Four irradiation experiments using **FHP-Linker** were performed at increasing magnetic stirring rates. Each irradiation was performed for four hours and after each irradiation experiment, the cleavage efficiency was determined using a standard Fmoc quantification analysis (Figure 3).[33, 34] This analysis showed that increasing the stirring rate improves cleavage efficiency. Stirring at 1060 rpm for four hours provided a cleavage of over 80%. The integrity of the beads was visualized by microscopy and showed that increasing the stirring rate enhanced the deformation of the beads (Figure 3A). It is possible that elevated stirring rates improve the exposure of the particles to the UV light that leads to an increase in cleavage efficiency. Another option is that by increasing the magnetic stirring rate we are applying stronger compressive forces on the beads which grind them to smaller particles with larger surface area. Such process will expose more photolinker to the light which suggests that the photocleavage efficiency depends on the size of the beads rather than on the mixing rate itself.

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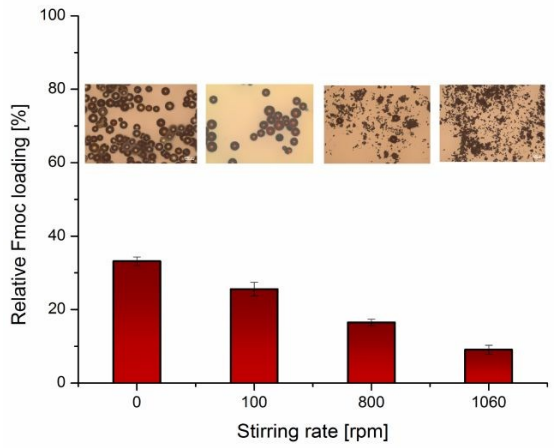

Figure 3. Irradiation of **FHP-Linker** at increasing stirring rate enhanced cleavage efficiency and the grinding of the solid support beads.

Time-dependent photocleavage efficiency.

We checked what will be the time required to achieve optimal photocleavage. We irradiated **FHP-Linker** at 1060 rpm for one up to six hours (Figure 4). Cleavage efficiency was determined by Fmoc quantification of the beads after irradiation. The cleavage after six hours reached over 80%. As an orthogonal analysis, the amount of cleaved *N*-Cbz-*O*-Fmoc-hexanolamine **3** in the filtrate was quantified by UV spectroscopy.

To achieve this, **3** was synthesized in solution and diluted to provide standard solutions at different concentrations. These solutions were used to prepare a calibration curve to correlate between the concentration of **3** and absorbance at 301 nm. Measuring the UV absorbance of the filtrate solution after irradiation and fitting it to the calibration curve enabled us to determine the cleavage efficiency by different methods (Figure 4 and SI). There was a clear correlation between the cleavage efficiency determined by the amount of **3** in the filtrate to the one calculated by Fmoc quantification for the beads (Figure 4). The slightly lower cleavage yields calculated for the filtrate are probably because we applied only two DCM washes without shaking and some of the product remains inside the beads. The accurate quantitative method to evaluate the amount of cleaved material in the filtrate relies on the use of known standards and precise analytical protocol. It can be used to evaluate the efficiency of photocleavage setups or photolabile linkers. Considering the ongoing debate regarding the accuracy of Fmoc quantification protocols,[35] we feel that our analytical evaluation of the cleavage is a very good alternative.

To prove the applicability of the method to larger amount of solid support, we irradiated 100 mg of **FHP-Linker** for four hours, evaporated the filtrate solvent and took proton, and carbon NMR spectra of the cleaved compound **3** without any purification (SI). The NMR analysis showed a spectrum that matched to **3** that was synthesized in solution. HRMS and NMR proved that the new cleavage process can provide clean products. This also confirms that the process will afford enough material for biology studies.

The contribution of grinding the beads prior to photocleavage.

Four to six hours of irradiation is relatively short compared with common protecting groups removal protocols like hydrogenolysis using atmospheric hydrogen (8-16 h) but it is still long compared to standard solid phase cleavage duration like with TFA (1-4 h) or standard flow photocleavage (1-2 h). This might limit the number of irradiation experiments that can be performed in a typical workday. We decided to grind the beads prior to the irradiation in order to check the influence of beads size on cleavage efficiency. We stirred **FHP-Linker** beads for four hours at 1060 rpm without irradiation. The ground **FHP-Linker** beads were then irradiated only for one hour using 1060 rpm stirring. As a control, we irradiated **FHP-Linker** beads that were not pre-grinded under the same conditions. Fmoc quantification after irradiation of the pre-grinded beads showed that over 80% of the linker was cleaved off while in the control experiment only 40% was cleaved (Figure 5). Microscope analysis after irradiation showed that the pre-grinded samples contained particles that are much smaller in comparison with the control. Fluorescence microscopy images demonstrating bleaching of ground **FlAP-Linker** beads mesh after irradiation further demonstrate the difference that results from the cleavage protocol (SI).

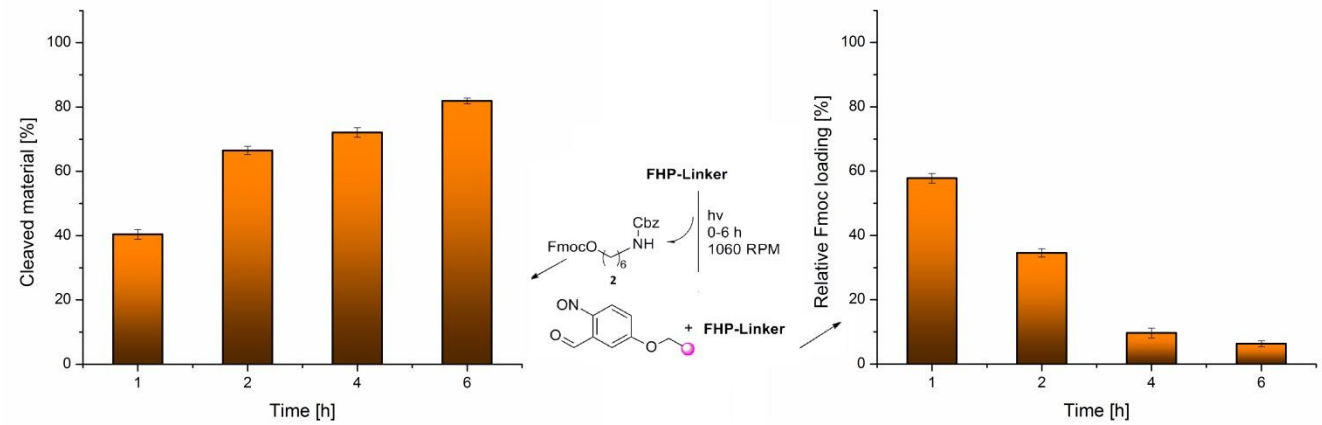

Figure 4. Irradiation time effect on cleavage efficiency. The efficiency of cleavage was evaluated by: Left) the quantity of cleaved compound **3** in the filtrate was calculated from absorbance calibration curve (SI). Right) the amount of linker left on the solid support was determined based on standard Fmoc quantification analysis.

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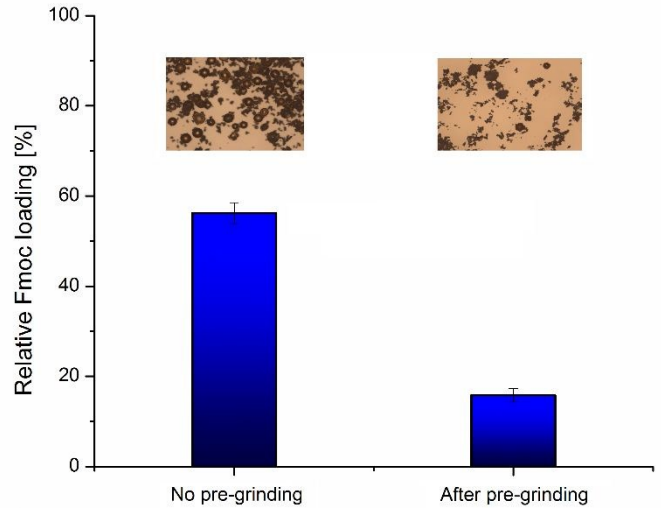


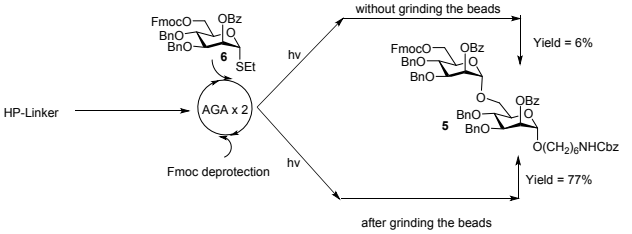
Figure 5. Irradiation of FHP-Linker with and without pre-grinding of the beads. This led to increase in cleavage efficiency. Grinding the beads four hours prior to one hour of irradiation significantly increased cleavage efficiency compared to the irradiation of intact beads.

Since irradiation time and stirring rate were identical in both experiments, it suggested that the increased surface area contributed to the great cleavage efficiency, and not only the stirring rate itself. To explore this effect, the active area of the irradiated particles was calculated based on the diameter measures in a microscope before and after grinding (SI). Our calculations show that grinding increases the active area by a magnitude of 80. This explains the ability to photocleavage more compound from the pre-grinded particles in 1 h that from intact beads in 4 h (Fig 3, 100 rpm compared with Fig 5, right). Achieving over 80% cleavage in only one hour of irradiation suggests that pre-grinding can be used as a routine to expedite the process and enable multiple experiments in a typical workday. To determine whether the mixing rate or the size of the beads is the crucial factor in photocleavage, irradiation of complete and ground beads was performed in identical conditions on a linear shaker at 210 rpm (SI) Unlike magnetic stirring, shaking does not grind the beads hence the size of the beads is maintained during the entire cleavage process.[33, 36] Although in both cases the mixing rate and time were identical, irradiation of ground beads in the shaker resulted in 58% cleavage while only 10.6% of the linker was cleaved off from intact beads. Since the efficiency in irradiating ground beads compared to complete ones was still significant, it confirms that the size of the beads and not the mixing rate is the detrimental factor in accelerating photocleavage. This suggests that photocleavage from ground beads instead of from intact ones might be advantageous also for other irradiation setups.

Synthesis of α-1-6-Mannose disaccharide and its removal from the support using the breaking beads approach.

The fully protected α-1-6-dimannose **5** was synthesized on the **FHP-Linker** using automated synthesizer glyconeer 2.1 (Scheme 2). **HP linker** was placed in the glyconeer 2.1 reaction vessel. The rest of the process was performed using typical automated glycan assembly (AGA) protocols.[19] Glycosylations of Fmoc protected thiomannoside **6** was performed using NIS/TfOH as activators at low temperature after which Fmoc was removed and another glycosylation cycle was performed using the exact conditions as the first one. We intentionally kept the Fmoc on the disaccharide to enable us to determine the efficiency of cleavage using spectroscopic analytical methods. After the second glycosylation, the solid support was removed from the reaction vessel and the quantity of Fmoc was determined. The calculated loading after AGA was 0.392 mmol/g because 30 % of the mass of the beads were attributed to the protected saccharide. Disaccharide **5** was cleaved off from the same amount of beads using two irradiation methods. Beads were irradiated either for one hour without stirring or while stirring at 1060 rpm after four hours of pre-grinding. After each cleavage, the amount of Fmoc that remains on the solid support was determined. The calculated Fmoc loading after irradiation without stirring was 0.376 mmol/g. This implies that only 6% of the disaccharide was cleaved. The calculated Fmoc loading determined following irradiation with stirring after pre-grinding the beads was 0.09 mmol/g. This shows that using the new cleavage protocol, 77%. We also calculated the cleavage yield by measuring the mass of **5** obtained after irradiation of beads with or without pre-grinding. The yield of photocleavage was 74.3% and 4.2% with and without grinding, respectively, which is in agreement with the efficiency determined by Fmoc monitoring. After irradiation of **5** using the breaking beads protocol, the crude filtrate was collected and analyzed by HPLC, NMR, and MS showing a purity of over 95%. Disaccharide **5** contains eight aromatic moieties and is a good model for a typical oligosaccharide synthesized on such linkers.[17, 29, 37] The irradiation studies performed on disaccharide **5** confirms that the new strategy is applicable for complex compounds and further highlights the profound advantage of the new cleavage strategy.

In all our studies, browning of the resin was observed during irradiation. Browning of polystyrene beads is a known phenomenon that probably results from the formation of nitrosoaldehyde during photocleavage.[38] Such moiety, which absorbs UV light, might decrease the efficiency of photocleavage overtime.[38]



Scheme 2: Synthesis of disaccharide by AGA. The disaccharide was synthesized on **HP-Linker** in glyconeer 2.1 from two monomers by performing one cycles of glycosylation/deprotection followed by a second glycosylation. Afterwards, the saccharide cleaved by UV irradiation with and without grinding the beads prior to irradiation.

However, by grinding the beads prior to irradiation we make sure that the surface area is large enough to minimize the effect of browning on photocleavage. The accuracy of our calculated cleavage efficiency using three orthogonal methods proves that the browning does not play a crucial role when our method is used. Although the nature of the Merrifield polystyrene resin itself might also contribute to this phenomenon, replacing it with another solid support might hamper its applicability for peptide and oligosaccharide synthesis. Using smaller beads with a higher amount of light accessible surface area.

As a note, the exact irradiation efficiency might be setup-dependent. Although there might be variability when the cleavage will be performed by the similar setup in other labs, the differences between irradiation of beads with and without grinding were reproduced multiple times. Furthermore, we demonstrated that the grinding effect was detrimental for both stirrer and shaker setups, proving the validity and generality of the observation. It is logical to think that the presence of UV active moieties on peptides or saccharides might decrease the efficiency of irradiation. However, photocleavage of biopolymers have been demonstrated even with up to hundreds of UV active moieties.[28, 29] The effect of grinding the beads will not have any negative effect on the efficiency. In contrast, as demonstrated for disaccharide **5**, the enhanced exposure will make sure that the process still surpasses the common strategies and might provide an advantage when many UV absorbing groups are present. Many reports in the past failed to reach efficient cleavage yields. Most of these methods rely on very powerful setups sometimes apply filters or rely on expensive flow systems.[6, 14-16, 19, 25] We rely on a LED lamp with a specific wavelength, do not use any filters and the setup is as simple as it gets. Still, we managed to get reproducible and high yield cleavage. Moreover, since we use a batch reactor, we do not risk any clogging and can also stop for checking the progress at any time.

Conclusions

In summary, a new approach to cleave compounds from photolabile linkers on solid support was described. A simple combination of a benchtop LED irradiation and magnetic stirring provides efficient photocleavage. By using a number of complementary analytical techniques, we showed that increasing the surface area of the polystyrene beads by grinding expedite photocleavage. The strategy was demonstrated for a fully protected oligosaccharide model, which proves that it is straightforward, applicable for bio relevant targets, and can be done in any standard laboratory. This can make the use of photolabile linkers more accessible to the community. The method can be very valuable for cleaving complex molecules from photolabile linkers in high efficiency.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Prof. Meital Reches for microscopy analysis and Prof. Shlomo Yitzchaik for LED irradiation system.

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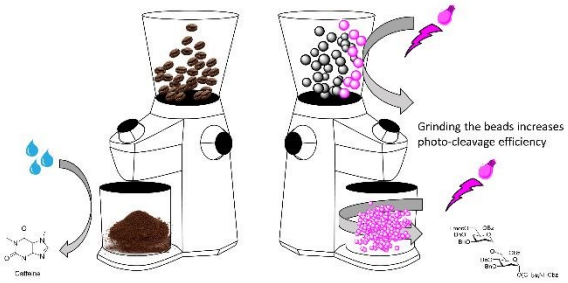

TOC entry text : Grinding of polystyrene beads accelerates photocleavage