RESEARCH ARTICLE

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A pH-Triggered Polymer Degradation or Drug Delivery System by Light-Mediated *Cis/Trans* Isomerization of *o*-Hydroxy Cinnamates

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A new methodology for the pH-triggered degradation of polymers or for the release of drugs under visible light irradiation based on the cyclization of *ortho*-hydroxy-cinnamates (*o*HC) to coumarins is described. The key *o*HC structural motif can be readily incorporated into the rational design of novel photocleavable polymers via click chemistry. This main-chain moiety undergoes a fast photocleavage when irradiated with 455 nm light provided that a suitable base is added. A series of polyethylene glycol-*alt*-*ortho*-hydroxy cinnamate (polyethylene glycol (PEG)$_n$-*alt*-*o*HC)-based polymers are synthesized and the time-dependent visible-light initiated cleavage of the photoactive monomer and polymer is investigated in solution by a variety of spectroscopic and chromatographic techniques. The photo-degradation behavior of the water-soluble poly(PEG$_{2000}$-*alt*-*o*HC) is investigated within a broad pH range (pH = 2.1–11.8), demonstrating fast degradation at pH 11.8, while the stability of the polymer is greatly enhanced at pH 2.1. Moreover, the neat polymer shows long-term stability under daylight conditions, thus allowing its storage without special precautions. In addition, two water-soluble PEG-based drug-carrier molecules (mPEG$_{2000}$-*o*HC-benzhydrol/phenol) are synthesized and used for drug delivery studies, monitoring the process by UV–vis spectroscopy in an ON/OFF intermittent manner.

1. Introduction

Since the inception of polymer science, chemists strived to design stimuli-responsive macromolecules, also referred to as "smart" polymers, which have gained interest from industry and academia alike. The exposure of the material to environmental changes such as temperature, pH, redox, enzyme, voltage, gas, mechanical force, and light causes alterations in the physical and chemical properties, which leads to changes in dimensions, aggregation states, interactions, as well as structures.[1] Among those stimuli, light has attracted the most attention due to its availability, high efficiency, clean character, and the possibility for easy spatiotemporal control.[2,3] Light-induced processes that start/stop by switching on/off the light not only produce fewer by-products as no additional reagents are involved, but also allow the tuning of relevant parameters such as light intensity or irradiation time and wavelength. In this context, light-cleavable polymers are of special value:[3] Their ability to easily degrade into smaller fragments upon irradiation bears the promise for many applications including drug release,[4] biomacromolecule delivery, nanocontainers, and self-healing materials.[5] Ideally such polymers should be cleavable by visible rather than UV light to allow better compatibility especially with biological materials, but at the same time should be stable under daylight conditions to allow long-term storage without the necessity for special precautions.

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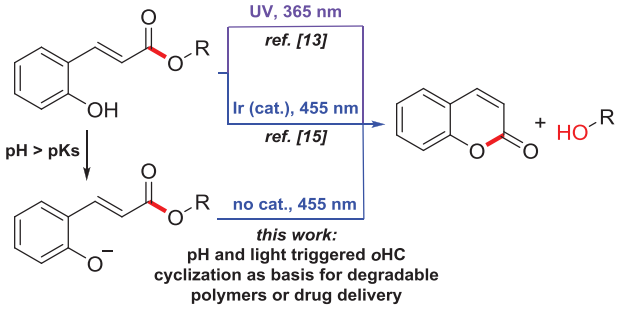


Figure 1. Commonly used strategies for photo mediated synthesis of coumarins.

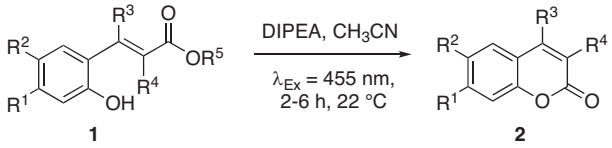
Coumarins and their derivatives[6] are known for their biological applications, such as antitumor,[7] antioxidant,[8] anti-HIV[9] as well as for their utilization as sensitizers,[10] for fluorescent sensors[11] and light-emitting diodes.[12] They can be synthesized by cyclization of *ortho*-hydroxy-*(Z)*-cinnamates, while the corresponding *ortho*-hydroxy-(*E*)-cinnamates are also suitable starting materials but require a preceding E/Z-double bond isomerization. However, there are only few reports to achieve this isomerization photochemically, either initiated by UV-light[13] or mediated by visible light utilizing organic[14] or noble transition-metal based photocatalysts (**Figure 1**).[15]

Herein, we report that this transformation can be triggered under basic conditions (i.e., pH > pK_a of the phenolic residue) in the visible light region of the spectrum, notably without the necessity of employing any photocatalyst. Based on this strategy, novel *ortho*-hydroxy-cinnamates (*o*HC)-bis(alkyne)-based monomers suitable for click chemistry are developed, which can be transformed to stimuli-responsive polymers allowing its degradation at basic pH under visible light irradiation.

Photo-cleavable polymers contain metastable photo-responsive groups, which maintain their properties without external stimuli. However, upon light irradiation, these groups can break from the polymer initiating the degradation process of the macromolecule. The two main categories for the subdivision of light-cleavable polymers place the chromophores either in the sidechain of the polymer or in the main-chain, directly onto the backbone. To date, the leading photocleavable main-chain groups are truxillic acid and *o*-nitrobenzyl, which degrade into cinnamates and *o*-nitrosobenzylaldehydes, respectively.[2] Since the irradiation with "hard UV-light" for these photo-responsive groups is necessary, it limits their biological applications.

More compatible would be the photodegradation triggered by visible light, which poses the challenge to avoid a background process, given the ubiquitous presence of this stimulus. Thus, we set out to develop a system that can be degraded by visible light but only upon an initial activation: Featuring *o*HC as a photocleavable unit within a polymer, we report here their catalyst free, efficient degradation under visible light conditions upon adjusting the pH to >7. We began our investigation questioning whether deprotonation of the acidic phenolic hydroxy group (pK_a = 10) could enhance the push-pull character of the conjugated system resulting in a redshift of the absorbance, which would allow the direct activation of the molecule by visible light.

Table 1. Catalyst free, visible light mediated coumarin synthesis.



1a/2a: $R^1 = R^2 = R^3 = R^4 = H$; $R^5 = Et$ (92 %)
1b/2b: $R^1 = OH$; $R^2 = R^3 = R^4 = H$; $R^5 = Et$ (93 %)
1c/2c: $R^1 = R^2 = R^3 = H$; $R^4 = Me$; $R^5 = Et$ (96 %)
1d/2d: $R^1 = OH$; $R^2 = R^3 = H$; $R^4 = Me$; $R^5 = Et$ (99 %)
1e/2e: $R^1 = R^2 = R^4 = H$; $R^3 = Me$; $R^5 = Et$ (80 %)
1f/2f: $R^1 = R^2 = R^3 = H$; $R^4 = CH_2CHCH_2$; $R^5 = Et$ (98 %)
1g/2g: $R^1 = OCH_2CCH$; $R^2 = R^3 = R^4 = H$; $R^5 = CH_2CCH$ (98 %)

Entry[a)]	Substrate	Conditions	Conversion [%][b)]
1	**1a**	No DIPEA	N.R.
2	**1a**	DIPEA, no irradiation	N.R.
3	**1a**	DIPEA	100
4	**1a**	tBuOK instead of DIPEA	100

[a)] Reaction conditions: 0.25 mmol **1a–1g**, DIPEA (20 mol%) in 1 mL MeCN. Irradiation with λ = 455 nm for 2–6 h; [b)] Based on ^{1}H NMR. Abbreviation: N.R. = no reaction detected.

2. Results and Discussion

Choosing **1a** as a model substrate (**Table 1**), we established that indeed no formation of the coumarin product **2a** is observed either upon irradiation at 455 nm without the addition of base N,N-diisopropylethylamine (DIPEA) or in the presence of a base without irradiation (entries 1, 2). In contrast, full conversion to **2a** could be achieved when substoichiometric amounts of DIPEA (20 mol%, entry 3) or ^{t}BuOK (20 mol%, entry 4) were used. These results are in line with UV–vis spectroscopy data of **1a** (Figure S10, Table S1, Supporting Information), showing a bathochromic shift from ≈390 to 470 nm when moving from acidic (pH 2.1) to basic (pH 11.8) conditions. Under the optimized conditions, substrates **1b–1g** could also be transformed to the corresponding coumarins **2b–2g** upon irradiation at 455 nm (Table 1), going along with a bathochromic shift upon addition at DIPEA (Figure S10, Supporting Information). Remarkably, substrates **1f** and **1g**, were converted almost quantitatively into the desired compounds **2f** and **2g** with no signs of cross reactivity that could have been caused by the extra double or triple bond.

Having established the facile cyclization of *o*HCs through the combination of basic pH and visible light, we envisioned the possibility of applying this concept to the design of novel photo-cleavable main-chain polymers. Thus, poly(polyethylene glycol-*alt*-*ortho*-hydroxy cinnamate, polyethylene glycol (PEG)$_n$-*alt*-*o*HC) **3a** with short PEG_{200} chains to allow the detailed analysis of the polymer and its degradation product by ^{1}H NMR analysis (Figure S1A,B, Supporting Information) was assembled via copper(I)-catalyzed azide alkyne cycloaddition "click" reaction of *o*HC-bis(Alk) **1g** and PEG_n-diazides (**Figure 2**, left). Analogously, the synthesis of a water-soluble polymer **3b** featuring PEG_{2000} chains (M_W = 56.3 k (PDI of 2.2) estimated by GPC)

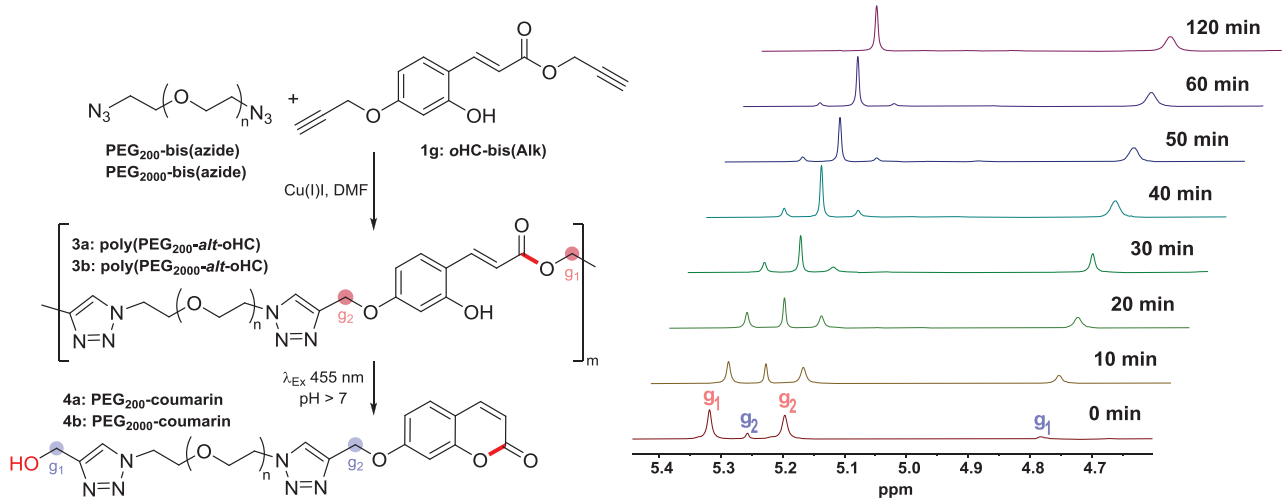


Figure 2. Left: Synthesis and visible light mediated photodegradation of **3a/3b**; reaction conditions: **1g**, PEG_n-bis(azide), CuI, DMF, 70 °C, 16 h. Right: Time-dependent photocyclization of **3b** followed by ^1H NMR spectroscopy monitoring the CH_2 (g_1/g_2) junctions (for detailed information see Figure S1, Supporting Information).

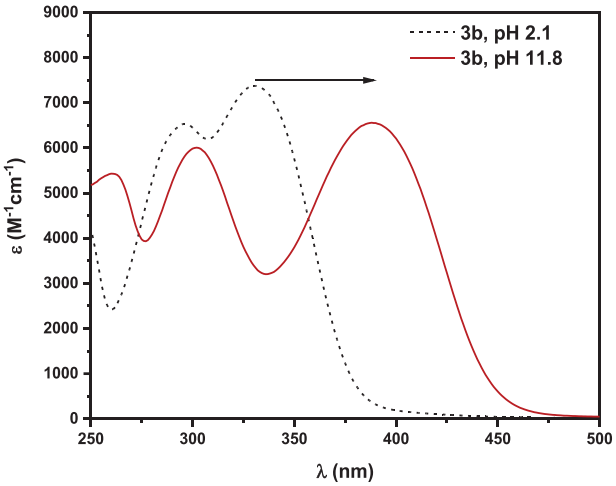


Figure 3. UV–vis spectra of **3b** in 0.1 M HCl/KCl buffer pH 2.1 and 0.1 M Britton–Robinson buffer pH 11.8.

was readily achieved. UV–vis spectroscopy confirmed the ability of the molecule to absorb visible light upon pH-change due to a bathochromic shift (**Figure 3**). Under acidic pH-values, $\lambda^{(1)}_{max}$ is located at 330 nm compared to basic conditions under which a $\lambda^{(1)}_{max}$ value of 384 nm fading into the visible light region was observed (Figure 3).

For benchmark purposes, we established that the photocyclization of monomer **1g** and polymer **3a** to its coumarin counterparts **2g** (Figure S3, Supporting Information) and **4a** (Figure S4, Supporting Information) in the presence of DIPEA can be conveniently analyzed by ^1H NMR spectroscopy, monitoring for **3a** the disappearance of the CH_2-junction groups (Figure 2, blue/red circles) and the appearance of the benzylic protons of the cleaved triazole unit in **4a**. Full cleavage was achieved within 40 min of irradiation at 455 nm LED light for both compounds (Figure S5, Supporting Information). The photo-initiated degradation of the water-soluble polymer **3b**, thus potentially relevant for biological applications, was subsequently investigated at five different pH values (pH = 2.1, 5.5, 6.5, 7.4, and 9.2), which were specifically selected to simulate those found at the digestive system, intracellular acidic pH, cancer cells, physiological pH, and colon, respectively. The pK_a of 8.6 was determined for **3b** by UV–vis spectroscopy monitoring the pH dependent formation of its corresponding alkoxide (Figure S8, Supporting Information). The shelf stability of the polymer **3b** was analyzed by ^1H NMR spectroscopy with regard to the formation of **4b**. The material was stored under exclusion of light for ten months and on a working bench under daylight exposure in an Eppendorf cup for five days. In both cases no degradation of the material **3b** was observable.

The photoinduced cleavage in **3b** could not only be monitored by NMR spectroscopy (Figure 2, right) following the lines established for **3a**, but also by UV–vis, fluorescence spectroscopy, or GPC analysis.

Representative illustrations are provided in **Figure 4**, full details can be found in the Supporting Information. In line with our model study (cf. Table 1), the photocleavage of **3b** to the corresponding coumarin **4b** is pH-dependent, reaching full conversion after 20 min at pH 9.2, after 30 min at physiological pH 7.4, and after 120 min at slightly acidic pH 6.5. In contrast, for the photocleavage process at pH 2.1 only 30% conversion was reached after 120 min of irradiation (Figure 4A; Figure S6, Supporting Information). As an alternative application we envisioned that water-soluble and photocleavable drug-carrier molecules can be developed. The design was based on the combination of methylated PEG (M_n = 2000) for enhanced water solubility and an *ortho*-hydroxycinnamate core as the alcohol uncaging group. The synthesis of **5** was carried out with readily available synthons (see Scheme S3, Supporting Information), aiming at the release of phenol and diphenylmethanol serving. This selection simulated both phenolic drugs (e.g., propofol, tetrahydrocannabinol, cannabidiol, morphine, buprenorphine, nalbuphine, etorphine, etc.) and benzylic alcohol containing drugs (e.g., terfenadine, ancymidol, fesoterodine, mefloquine, halofantrine, quinine, etc.).

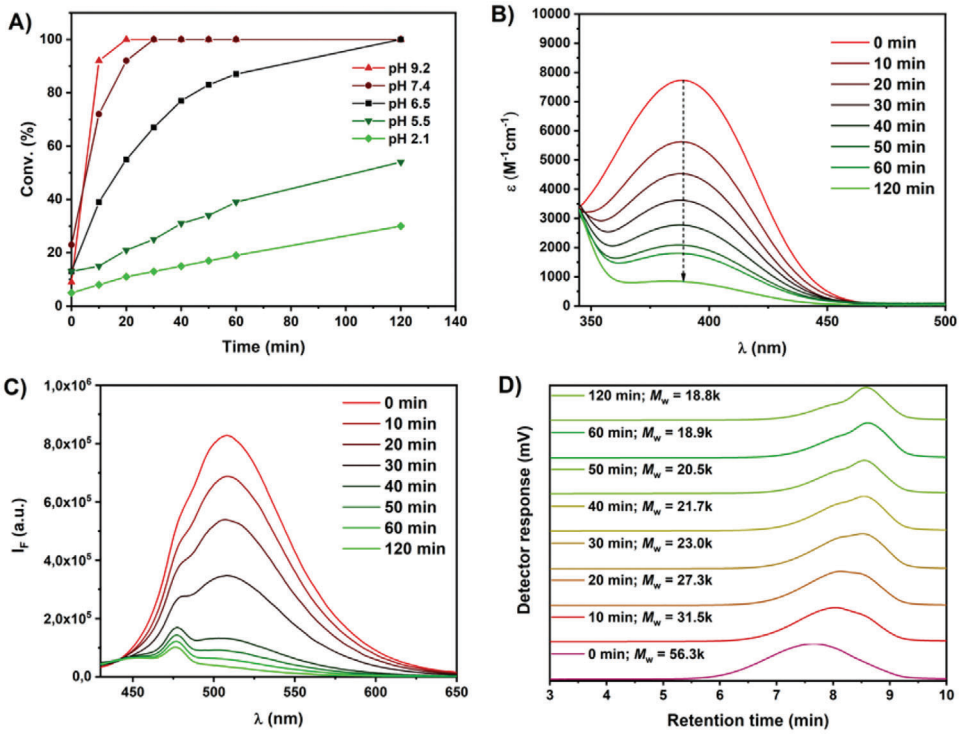


Figure 4. Photocleavage process of **3b** A) at different pH levels using 0.1 M carbonate buffer (pH 9.2), 0.01 M PBS buffer (pH 7.4, 6.5, and 5.5) and 0.1 M HCl/KCl buffer (pH 2.1); determined by ^{1}H NMR, B) in 0.01 M PBS buffer (pH 6.5) monitored by UV–vis spectroscopy, C) in 0.01 M PBS buffer (pH 6.5) monitored by fluorescence spectroscopy exciting at 410 nm, and D) in 0.01 M PBS buffer (pH = 6.5) monitored by GPC. GPC traces showing a decrease in molecular weight (M_W) with increasing irradiation time.

5a and **5b** were subjected to a photocleavage process under visible light irradiation in an ON/OFF intermittent manner at physiological pH 7.4 in 0.01 M phosphate-buffered saline (PBS) buffer. Fast release of the alcohol from either **5a** or **5b** should only occur upon a photo-triggered *trans*-to-*cis* isomerization followed by cyclization, and it should stop when the irradiation is interrupted and only resume when the light stimulus is reapplied. In order to demonstrate this behavior, we monitored the absorbance of **5a/5b** in response to periodic light irradiation at $\lambda = 455$ nm (Figure S9, Supporting Information) as well as in dark as a control-experiment.

Indeed, when the irradiation was turned on for 1 min, a rapid decrease for the characteristic peak of the phenolate at 391 nm in the absorbance spectra was observed, indicating again the successful coumarin formation with concurrent alcohol release. Furthermore, when the irradiation was switched off, the process also stopped as indicated by no change in the absorbance over a 2 min time period (**Figure 5**).

3. Conclusions

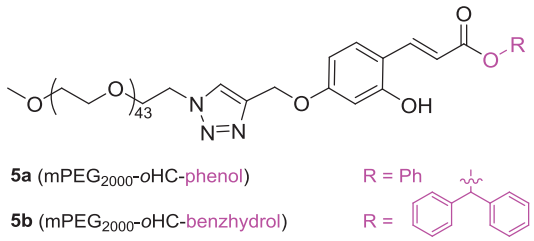
In conclusion, we have demonstrated that a variety of coumarins can be easily synthesized in almost quantitative yields via a catalyst free, visible light mediated isomerization/cyclization sequence, taking advantage of a UV-to-vis bathochromic shift of *o*HC under basic conditions. This methodology enables the preparation of dual pH- and photo-responsive (PEG$_n$-*alt*-*o*HC)-based polymers, which undergo a controlled photocleavage under exposition to visible light at slightly basic pH. This approach was applied to both non-water- and water-soluble polymers in two proof of concept studies toward degradable polymers and drug delivery. Further studies to ensure full biocompatibility of the fragments generated are currently under way aiming at applications in medicinal chemistry. Other fields such as lithography, polymer cross-linking, or biotechnology might benefit from this methodology as well.

4. Experimental Section

General Procedure for the Synthesis of Coumarins 2: In an 8 mL vial equipped with a magnetic stir bar 2-hydroxy cinnamates **1** (0.25 mmol) and 20 mol% DIPEA in acetonitrile (1 mL) were added. The vial was closed with a septum and subjected to three freeze-pump-thaw cycles for degassing and subsequently irradiated with a LED (λ_{Ex} = 455 nm) for 4 h. Evaporation of the solvent and purification on silica (hexanes/EtOAc) gave the desired compound **2**.

*Photocleavage of **3b** to **4b** Monitored by ^{1}H NMR*: In a septum-sealed vial equipped with a magnetic stirrer **3b** (100 mg) in a suitable buffer (2 mL) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.2 mL samples were collected into Eppendorf cups during a given time interval. The collected samples were freeze-dried until complete removal of water, dissolved in 0.6 mL of $CDCl_3$ and the soluble part was subjected to ^{1}H NMR spectroscopy. The shift of $\mathbf{g_1}$ and $\mathbf{g_2}$ peaks (Figures S1, S6, Supporting Information) was monitored over time.

^{1}H NMR of the corresponding degradation product **4b** after irradiation: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83 (s, 1H), 7.64 (d, J = 9.5 Hz,



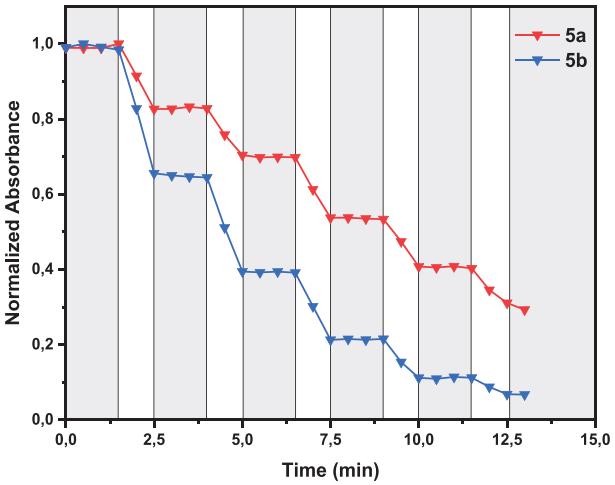


Figure 5. Normalized UV absorption of **5a/5b** at 391 nm after irradiation with visible light (λ = 455 nm) in 0.01 M PBS buffer (pH = 7.4) in an off and on intermittent manner.

1H), 7.39 (d, J = 9.2 Hz, 1H), 7.00–6.85 (m, 2H), 6.26 (d, J = 9.5 Hz, 1H), 5.26 (s, 2H), 4.78 (s, 2H), 4.56 (dt, J = 8.1, 5.0 Hz, 4H), 3.94–3.81 (m, 4H), 3.77–3.45 (m, 186H).

*Photocleavage of **3b** to **4b** Monitored by UV–vis Spectroscopy*: In a septum-sealed vial equipped with a magnetic stirrer 100 mg of **3b** in 2 mL 0.1 M Britton–Robinson buffer (pH = 6.50) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.20 mL samples were taken in a 10 min interval for 60 min and one last sample at 120 min and filled up to 1 mL with 0.1 M Britton–Robinson buffer (pH = 11.8) and used as stock solutions. The samples were diluted with 0.1 M Britton–Robinson buffer (pH = 11.8) to 62 μM and were measured.

*Photocleavage of **3b** to **4b** Monitored by Fluorescence Spectroscopy*: In a septum-sealed vial equipped with a magnetic stirrer 100 mg of **3b** in 2 mL 0.1 M Britton–Robinson buffer (pH = 6.5) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.20 mL samples were taken in a 10 min interval for 60 min and one last sample at 120 min and filled up to 1 mL with 0.1 M Britton–Robinson buffer (pH = 11.8) and used as stock solutions. The samples were diluted with 0.1 M Britton–Robinson buffer (pH = 11.8) to 1.55 nM and measured.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords

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[1] a) C. Lu, M. W. Urban, *Prog. Polym. Sci.* **2018**, *78*, 24; b) Z.-Q. Cao, G.-J. Wang, *Chem. Rec.* **2016**, *16*, 1398; c) X. Fu, L. Hosta-Rigau, R. Chandrawati, J. Cui, *Chem* **2018**, *4*, 2084; d) M. Wei, Y. Gao, X. Li, M. J. Serpe, *Polym. Chem.* **2017**, *8*, 127.

[2] Q. Yan, D. Han, Y. Zhao, *Polym. Chem.* **2013**, *4*, 5026.

[3] O. Bertrand, J.-F. Gohy, *Polym. Chem.* **2017**, *8*, 52.

[4] A. Paul, M. Bera, P. Gupta, N. D. P. Singh, *Org. Biomol. Chem.* **2019**, *17*, 7689.

[5] a) J.-M. Schumers, C.-A. Fustin, J.-F. Gohy, *Macromol. Rapid Commun.* **2010**, *31*, 1588; b) D. Habault, H. Zhang, Y. Zhao, *Chem. Soc. Rev.* **2013**, *42*, 7244; c) N. Fomina, C. L. Mcfearin, M. Sermsakdi, J. M. Morachis, A. Almutairi, *Macromolecules* **2011**, *44*, 8590; d) B. Yan, J.-C. Boyer, D. Habault, N. R. Branda, Y. Zhao, *J. Am. Chem. Soc.* **2012**, *134*, 16558.

[6] a) S. Ahadi, M. Zolghadr, H. R. Khavasi, A. Bazgir, *Org. Biomol. Chem.* **2013**, *11*, 279; b) K. B. Manjappa, J.-M. Lin, D.-Y. Yang, *J. Org. Chem.* **2017**, *82*, 7648; c) R. F. Guíñez, M. J. Matos, S. Vazquez-Rodriguez, L. Santana, E. Uriarte, C. Olea-Azar, J. D. Maya, *Future Med. Chem.* **2013**, *5*, 1911.

[7] a) M. Kumar, R. Singla, J. Dandriyal, V. Jaitak, *Anti-Cancer Agents Med. Chem.* **2018**, *18*, 964; b) M.-M. Liu, X.-Y. Chen, Y.-Q. Huang, P. Feng, Y.-L. Guo, G. Yang, Y. Chen, *J. Med. Chem.* **2014**, *57*, 9343; c) M. Musa, J. Cooperwood, M. O. Khan, *Curr. Med. Chem.* **2008**, *15*, 2664.

[8] a) G. Borges Bubols, D. Da Rocha Vianna, A. Medina-Remon, G. von Poser, R. Maria Lamuela-Raventos, V. Lucia Eifler-Lima, S. Cristina Garcia, *Mini-Rev. Med. Chem.* **2013**, *13*, 318; b) I. Kostova, *Mini-Rev. Med. Chem.* **2006**, *6*, 365; c) M. Salem, M. Marzouk, A. El-Kazak, *Molecules* **2016**, *21*, 249; d) G. Mazzone, N. Malaj, A. Galano, N. Russo, M. Toscano, *RSC Adv.* **2015**, *5*, 565.

[9] a) L. Xie, Y. Takeuchi, L. M. Cosentino, A. T. Mcphail, K.-H. Lee, *J. Med. Chem.* **2001**, *44*, 664; b) D. Yu, M. Suzuki, L. Xie, S. L. Morris-Natschke, K.-H. Lee, *Med. Res. Rev.* **2003**, *23*, 322.

[10] a) J. Zhou, Q. Liu, W. Feng, Y. Sun, F. Li, *Chem. Rev.* **2015**, *115*, 395; b) S. Ji, H. Guo, W. Wu, W. Wu, J. Zhao, *Angew. Chem., Int. Ed.* **2011**, *50*, 8283.

[11] a) X. Liu, J. M. Cole, Z. Xu, *J. Phys. Chem. C* **2017**, *121*, 13274; b) T. Shiraishi, H. Kagechika, T. Hirano, *New J. Chem.* **2015**, *39*, 8389.
[12] a) T. Song, G. Zhang, Y. Cui, Y. Yang, G. Qian, *CrystEngComm* **2016**, *18*, 8366; b) Z. Feng, Y. Yu, X. Yang, D. Zhong, D. Song, H. Yang, X.i Chen, G. Zhou, Z. Wu, *Inorg. Chem.* **2019**, *58*, 7393; c) M.-Y. Chang, Y.-K. Han, C.-C. Wang, S.-C. Lin, Y.-J. Tsai, W.-Y. Huang, *J. Electrochem. Soc.* **2008**, *155*, J365.
[13] a) T. Horaguchi, N. Hosokawa, K. Tanemura, T. Suzuki, *J. Heterocycl. Chem.* **2002**, *39*, 61; b) N. Gagey, P. Neveu, C. Benbrahim, B. Goetz, I. Aujard, J.-B. Baudin, L. Jullien, *J. Am. Chem. Soc.* **2007**, *129*, 9986.
[14] a) T. Neveselý, C. G. Daniliuc, R. Gilmour, *Org. Lett.* **2019**, *21*, 9724; b) J. B. Metternich, R. Gilmour, *J. Am. Chem. Soc.* **2016**, *138*, 1040.
[15] K. Zhan, Y. Li, *Catalysts* **2017**, *7*, 337.

