



Photochemical Access to Substituted β -Lactams and β -Lactones via the Zimmerman-O'Connell-Griffin Rearrangement

Downloaded from: <https://research.chalmers.se>, 2025-12-09 00:06 UTC

Citation for the original published paper (version of record):

Runemark, A., Martos, M., Nigríni, M. et al (2023). Photochemical Access to Substituted β -Lactams and β -Lactones via the Zimmerman-O'Connell-Griffin Rearrangement. *Organic Letters*, 25(29): 5520-5524.
<http://dx.doi.org/10.1021/acs.orglett.3c01990>

N.B. When citing this work, cite the original published paper.

Photochemical Access to Substituted β -Lactams and β -Lactones via the Zimmerman–O’Connell–Griffin Rearrangement

August Runemark, Mario Martos, Martin Nigrini, Francoise M. Amombo Noa, Lars Öhrström, and Henrik Sundén*



Cite This: *Org. Lett.* 2023, 25, 5520–5524



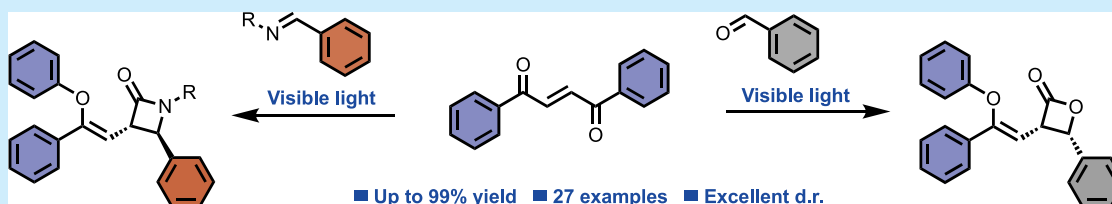
Read Online

ACCESS |

Metrics & More

Article Recommendations

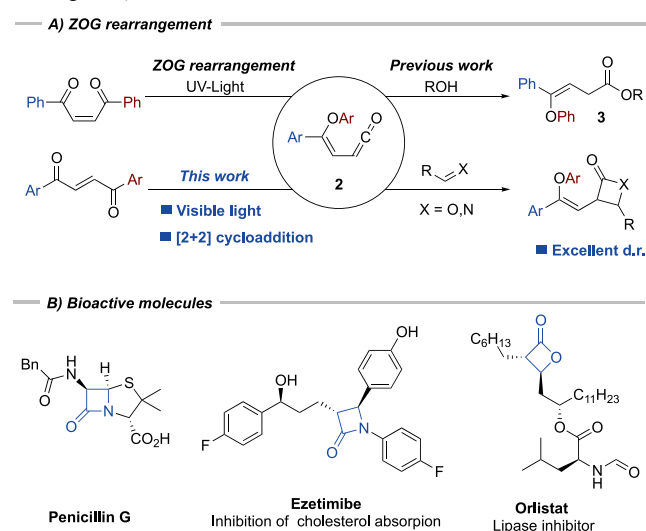
Supporting Information



ABSTRACT: A photomediated protocol giving facile access to substituted β -lactam and β -lactones is presented. The method realizes, for the first time, the use of the Zimmerman–O’Connell–Griffin (ZOG) rearrangement in [2 + 2] cycloaddition. Products are obtained in high yield with excellent diastereoselectivity under visible light irradiation and under mild reaction conditions.

β -Lactam and β -lactone rings stand out as key structural scaffolds found in many drugs and leading bioactive candidates (Scheme 1B). The most famous members of this family are

Scheme 1. Previous Work on the ZOG Rearrangement and Biologically Active Candidates



through clinical trials their important role as pharmaceutically interesting motifs.

Given the high importance of these classes of compounds, their syntheses have been thoroughly investigated. Most commonly, β -lactams are synthesized using the Staudinger synthesis, an imine-ketene [2 + 2] cycloaddition, and a range of different methods relying on this reaction have been developed.^{3,4} Ketenes are reactive compounds that typically are formed *in situ* from the α -deprotonation of acyl chlorides using a stoichiometric amount of base. This limits the structure of the ketenes and the reaction conditions available for the synthesis of β -lactams. An alternative method of producing ketenes *in situ* in a highly efficient manner is the photoinduced rearrangement of the dibenzoyl ethylene scaffold (1 in Scheme 1A), which was first discovered by Zimmerman, O’Connell, and Griffin in the 1960s (Scheme 1A).^{5–7} Despite thorough mechanistic investigations, this rearrangement has only been utilized in the synthesis of 4-oxo-butanoic esters and acids (3 in Scheme 1A) to date.^{8–12} Therefore, using the Zimmerman–O’Connell–Griffin (ZOG) rearrangement in combination with imines for the synthesis of substituted β -lactams is a novel and attractive strategy but potentially challenging. Typically, high-energy UV light is employed to carry out the ZOG rearrangement,^{5–7} and under these reaction conditions, several potential side reactions can occur, such as imine *E/Z*-

different penicillins, such as penicillin G. Another example is ezetimibe, a strong cholesterol absorption inhibitor and clinically proven reductant of plasma low-density lipoprotein fraction (LDL-C).¹ In turn, orlistat, containing a β -lactone ring, has found use as a lipase inhibitor and as a drug prescribed for weight loss.² These compounds, containing β -lactam and β -lactone rings as structural scaffolds, clearly show

Received: June 16, 2023

Published: July 18, 2023



isomerization and imine cycloadditions.^{13,14} A method relying on visible light could circumvent this problem, thereby making the ZOG rearrangement a powerful tool for the construction of four-membered rings under mild conditions.

Inspired by these opportunities, we initiated the study by choosing the model reaction between (*E*)-1,2-dibenzoyl ethylene **4** and the imine **5**. It is well established that upon irradiation with visible light, (*E*)-1,2-dibenzoyl ethylene undergoes isomerization to the *Z*-isomer **1**.¹⁵ We, therefore, envisaged that utilizing a high-intensity blue LED lamp as the irradiation source would make the isomerization go faster and be directly followed by the rearrangement reaction. To test this, a solution of 1,2-dibenzoyl ethylene (**4**) and imine **5** was irradiated with a 440 nm LED. After exploring various reaction conditions, it was discovered that the use of ethyl acetate as the solvent and a slight excess of the imine under ambient atmosphere led to the formation of the desired cycloaddition product **6** in 72% yield (Table 1, entry 4). While toluene did

Table 1. Optimization of the Photoinduced Synthesis of β -Lactams

entry	light source	solvent	5 (equiv)	yield 6 (%) ^a
1	440 nm LED	ethyl acetate	1.0	78
2	440 nm LED	toluene	1.0	90
3	440 nm LED	acetonitrile	1.0	51
4	440 nm LED	ethyl acetate	1.2	86 (72 ^b , 86 ^c)
5	525 nm LED	ethyl acetate	1.2	n.d.

^aYield determined by ¹H NMR using durene as the internal standard;

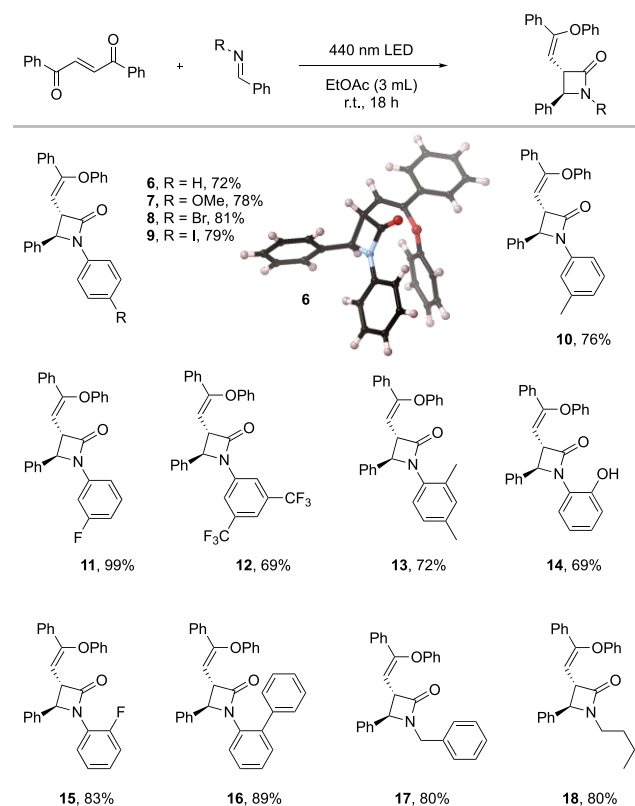
^bIsolated yield. ^cConducted on 1 mmol scale.

give a higher yield, the benefits of using a greener and more polar solvent made ethyl acetate the preferred choice for this reaction.^{16,17} To further optimize the reaction conditions, we tested different light sources. The blue LED (440 nm) was found to be effective in promoting both the isomerization and the rearrangement reaction, which led to the desired product formation in the optimized yield. However, the use of an LED with a longer wavelength, specifically 525 nm, did not promote the rearrangement reaction (Table 1, entry 5), which can be explained by the low absorbance of the (*Z*)-dibenzoyl ethylene at this wavelength (Figure S1).

With our optimized reaction conditions for the imine cyclization reaction obtained, a set of aryl–aryl imines was tested as reaction partners (Schemes 2 and 3). The introduction of electron-donating or electron-withdrawing groups in either the *para*, *meta*, or *ortho* position of the *N*-aryl group did not affect the reaction outcome significantly and gave the products **7**–**16** in 69–99% yield. Even the sterically demanding phenyl group in the *ortho* position was very well tolerated in the reaction and produced compound **16** in 89% yield. Imines with *N*-benzyl and *N*-butyl groups were also compatible with this methodology, which yielded both β -lactams **17** and **18** in 80% yield.

It is noteworthy that the compatibility with phenols gave product **14** in 69% yield. This illustrates the excellent selectivity toward the cyclization reaction over nucleophilic attack of the ketene intermediate by the phenol.

Scheme 2. Scope of *N*-Substituted Phenyl Imines and Single Crystal X-ray Structure of **6**^a

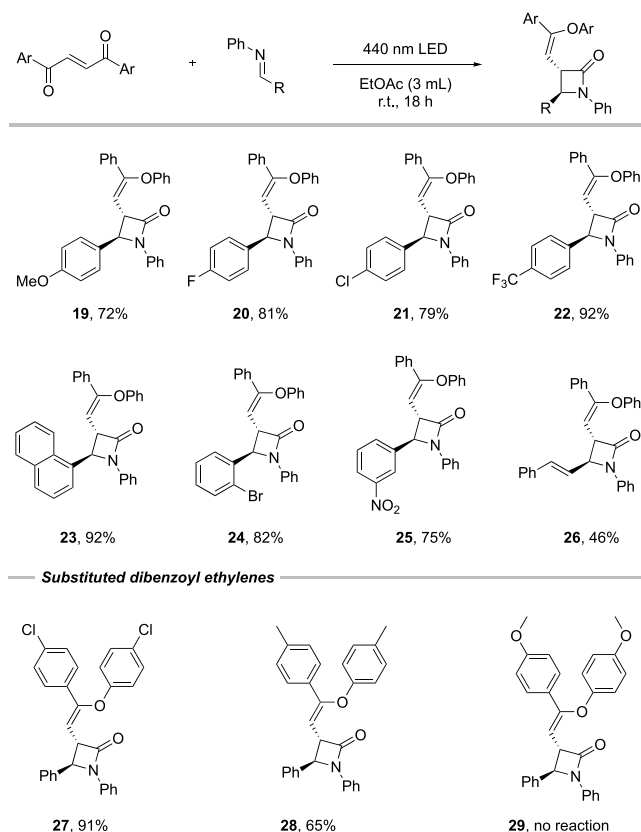


^aReaction conditions: **4** (0.1 mmol) and imine (0.12 mmol) in EtOAc (3 mL), 440 nm LED, 18 h. Isolated yield.

When the aldehyde group of the imine was changed by introducing electron-withdrawing or -donating functional groups, the reaction outcome was not significantly affected, thereby affording the products **19**–**26** in 46–92% yield. Compound **26** was obtained selectively, albeit in a diminished yield of 46%, over the potential competing [4 + 2] cycloaddition, which showcases the selectivity of the reaction. Furthermore, the 1,2-dibenzoyl ethylene can also be varied. When 1,2-dibenzoyl ethylene was substituted with chlorine or methyl in the *para* position of the phenyl rings, products **27** and **28** could be obtained in good yields. However, introduction of the strongly electron-donating methoxy group suppressed the reaction completely with no conversion of the 1,2-dibenzoyl ethylene starting material. This observation can be explained by the fact that the bis-*para*-methoxy dibenzoyl ethylene does not undergo isomerization from the *E*- to the *Z*-isomer under the present conditions. The use of unsymmetrical 1,2-dibenzoyl ethylenes, that is, where two different aryl groups on the alkene were installed, was shown to result in sluggish reaction mixtures with no selectivity of the aryl transfer. To further investigate this reactivity, the simpler nucleophile methanol was attempted, which resulted in similar results (for discussion, see the Supporting Information).

All the β -lactam products were obtained as single diastereomers, and the orientation of the substituents on the four-membered rings was determined to be in an *anti*-configuration by solving the crystal structure of compound **6** using single crystal X-ray diffraction (Scheme 2).

To investigate the generality of our efficient method for the synthesis of β -lactams, we turned our attention to the reaction

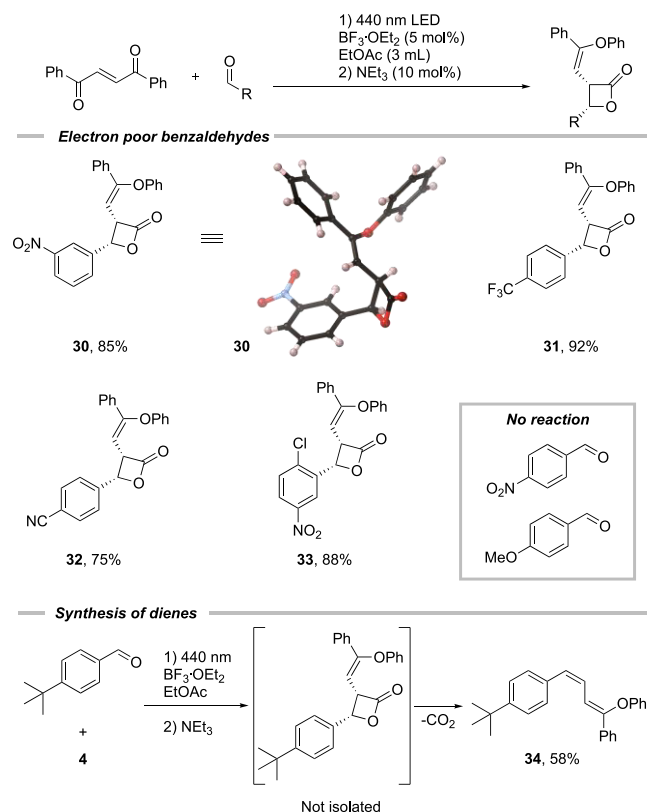
Scheme 3. Scope of Substituted *N*-Phenyl Imines^a

^aReaction conditions: dibenzoyl ethylene (0.1 mmol) and imine (0.12 mmol) in EtOAc (3 mL), 440 nm LED, 18 h. Isolated yield.

between 1,2-dibenzoyl ethylene and benzaldehydes. However, when we attempted the additive-free reaction between **4** and 3-nitro benzaldehyde under the conditions developed for the synthesis of β -lactams (Table S4, entry 1), no product was obtained. The addition of a Brønsted acid did not improve the results (Table S4, entry 2). However, we achieved successful synthesis of targeted lactone **30** with an 85% yield by employing boron trifluoride etherate and a suitable quenching procedure using triethylamine (Table S4, entry 4).

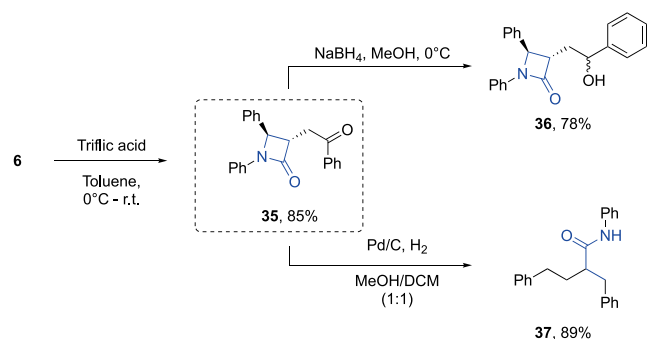
With an optimized procedure, different benzaldehydes were tested as substrates in the reaction (Scheme 4). Generally, electron-poor benzaldehydes gave the desired cycloaddition product in good to excellent yields (entries **30**–**33**), except for *para*-nitro benzaldehyde. Electron-rich benzaldehydes, however, were not tolerated and either did not take part in the cycloaddition reaction or decomposed rapidly via decarboxylation to yield the diene **34** in the case of *para*-*tert*-butyl benzaldehyde. The stereochemical outcome of the reaction was determined by single-crystal X-ray diffraction of compound **30**, and it was found that the lactones are formed with *syn* stereochemistry (Scheme 4).

To showcase the synthetic utility of the protocol, the reaction was performed on a 1 mmol scale to furnish model product **6** in 86% yield (Table 1, entry 4). Compound **6** was then further modified (Scheme 5). First, the phenoxy moiety could be hydrolyzed to reveal ketone **35** in 85% yield. Reduction of this compound with sodium borohydride gave alcohol **36** as a mixture of diastereomers in 78% yield. Compound **36** bears a structural resemblance to the pharmaceutically active drug ezetimibe, and the two-step

Scheme 4. Scope of Substituted Benzaldehydes and Single Crystal X-ray Structure of **30**^a

^aReaction conditions: (1) 1,2-dibenzoyl ethylene (0.1 mmol), substituted aldehyde (0.12 mmol), and $\text{BF}_3 \cdot \text{OEt}_2$ (5 mol %), 440 nm LED, 18 h under N_2 ; (2) Et_3N (10 mol %), 30 min. Isolated yield.

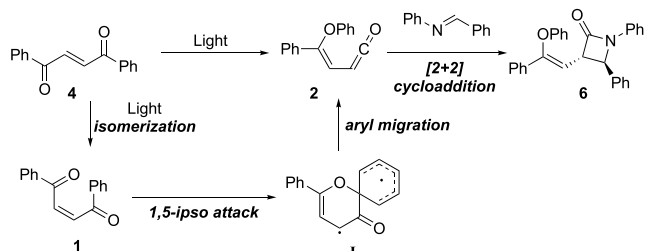
Scheme 5. Further Transformations



procedure developed in this work could be used to produce a variety of analogues of this drug (Scheme 1B). Hydrogenolysis of compound **35** with Pd/C and H_2 provided phenylpropylene amide **37**. The phenylpropylene backbone of **37** can be found in drugs such as trandolapril.¹⁸

The mechanism of the formation of the intermediate ketene has been thoroughly investigated in previous reports of this reaction and follows the pathway presented in Scheme 6. The *E*-1,2-dibenzoyl ethylene **4** is first isomerized to the *Z*-1,2-dibenzoyl ethylene **1**, which upon further excitation undergoes an intramolecular *ipso* attack of one of the oxygens to one of the phenyl rings.^{5,6,20,7–12,15,19} The formed spiro radical **I** collapses to form the ketene intermediate **2**, which is intercepted by an imine to form the final product via the

Scheme 6. Proposed Mechanism



Staudinger synthesis.^{21,22} To further support the formation of the ketene 2, ethanol was used as a nucleophile, thereby resulting in the formation of the butanoate ester (for discussion, see the Supporting Information).

In summary, the photomediated 1,5-aryl rearrangement of 1,2-dibenzoyl ethylenes, known as the Zimmerman–O’Connell–Griffin (ZOG) rearrangement, has proven to be a highly efficient method for synthesizing β -lactams and β -lactones. The developed protocol offers a readily accessible pathway to substituted β -lactams and β -lactones with excellent diastereoselectivity utilizing commercially available starting materials. The reported protocol demonstrates high yields and operational simplicity, and the diastereoselectivity is supported by the analysis of single-crystal X-ray diffraction of two representative examples. Considering the significance of β -lactams and β -lactones in medicinal chemistry, we firmly believe that this reaction holds significant potential, for instance, in the preparation of combinatorial libraries.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c01990>.

Experimental details and NMR spectra of synthesized compounds (PDF)

Accession Codes

CCDC 2258830–2258831 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Henrik Sundén – Department of Chemistry and Chemical Engineering, Chalmers University of Technology, 412 96 Gothenburg, Sweden; Department of Chemistry and Molecular Biology, University of Gothenburg, 412 96 Gothenburg, Sweden; orcid.org/0000-0001-6202-7557; Email: henrik.sunden@chem.gu.se

Authors

August Runemark – Department of Chemistry and Chemical Engineering, Chalmers University of Technology, 412 96 Gothenburg, Sweden; orcid.org/0000-0002-3650-1881

Mario Martos – Organic Chemistry Department and Institute of Organic Synthesis (ISO), University of Alicante, 03690 Alicante, Spain; orcid.org/0000-0001-7057-9618

Martin Nigrini – Department of Organic Chemistry, Faculty of Science, Charles University, 128 43 Prague, Czech Republic

Francoise M. Amombo Noa – Department of Chemistry and Chemical Engineering, Chalmers University of Technology, 412 96 Gothenburg, Sweden; orcid.org/0000-0001-8361-3432

Lars Öhrström – Department of Chemistry and Chemical Engineering, Chalmers University of Technology, 412 96 Gothenburg, Sweden; orcid.org/0000-0002-6420-2141

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.orglett.3c01990>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from the Swedish research council FORMAS (2019-00699): Wilhelm och Martina Lundgrens vetenskapliga stiftelse, “Grant Schemes at CU” (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935); and UA-Santander Movilidad 2022. We also thank the Olle Engkvist Foundation, Chalmers Areas of Advance Energy, Materials, Health, and Nano; and the Chalmers Materials Analysis Laboratory.

■ REFERENCES

- (1) Liu, Y.; Chen, J.-L.; Wang, G.-H.; Sun, P.; Huang, H.; Qing, F.-L. 4-CF₃-Ezetimibe Analogs: Design, Synthesis, and Biological Evaluation of Cholesterol Absorption Inhibitors. *Tetrahedron Lett.* **2013**, *54* (40), 5541–5543.
- (2) Pommier, A.; Pons, J.-M.; Kocienski, P. J. The First Total Synthesis of (–)-Lipstatin. *J. Org. Chem.* **1995**, *60* (22), 7334–7339.
- (3) Kamath, A.; Ojima, I. Advances in the Chemistry of β -Lactam and Its Medicinal Applications. *Tetrahedron* **2012**, *68* (52), 10640–10664.
- (4) Fu, N.; Tidwell, T. T. Preparation of β -Lactams by [2 + 2] Cycloaddition of Ketenes and Imines. *Tetrahedron* **2008**, *64* (46), 10465–10496.
- (5) Zimmerman, H. E.; Durr, H. G. C.; Lewis, R. G.; Bram, S. Mechanistic Organic Photochemistry. V.1 Phenyl Migration in a New Photochemical Reaction. *J. Am. Chem. Soc.* **1962**, *84* (21), 4149–4150.
- (6) Zimmerman, H. E.; Durr, H. G.; Givens, R. S.; Lewis, R. G. The Photochemistry of Dibenzoyl ethylenes. Mechanistic and Exploratory Organic Photochemistry. XXII. *J. Am. Chem. Soc.* **1967**, *89* (8), 1863–1874.
- (7) Griffin, G. W.; O’Connell, E. J. Photochemistry of Dibenzoyl ethylene; A Novel Photochemical Rearrangement and Reduction. *J. Am. Chem. Soc.* **1962**, *84* (21), 4148–4149.
- (8) Ghosh, A. Formation of an Exceptionally Stable Ketene during Phototransformations of Bicyclo[2.2.2]Oct-5-En-2-Ones Having Mixed Chromophores. *Beilstein J. Org. Chem.* **2020**, *16*, 2297–2303.
- (9) Kumar, C. V.; Murty, B. A. R. C.; Lahiri, S.; Chackachery, E.; Sciano, J. C.; George, M. V. Photochemical Transformations and Laser Flash Photolysis Studies of Dibenzobarrelenes Containing 1,2-Dibenzoylalkene Moieties. *J. Org. Chem.* **1984**, *49* (25), 4923–4929.
- (10) Maji, D.; Singh, R.; Mostafa, G.; Ray, S.; Lahiri, S. Topochemical Selectivity in Solid-State Photorearrangement: Conformational Control in Photorearrangements of Cis-1,2-Dibenzoylalkenes. *J. Org. Chem.* **1996**, *61* (15), 5165–5168.

- (11) Lahiri, S.; Dabral, V.; Chauhan, S. M. S.; Chakachery, E.; Kumar, C. V.; Scaiano, J. C.; George, M. V. Photochemical Transformations of Cis-1,2-Dibenzoylalkenes. *J. Org. Chem.* **1980**, *45* (19), 3782–3790.
- (12) Chanda, M.; Maji, D.; Lahiri, S. Solid-State Photolysis of Sterically Congested Cis-1,2-Dibenzoylalkenes: Isolation and Characterization of Vinylketenes. *Chem. Commun.* **2001**, *6*, 543–544.
- (13) Richardson, A. D.; Becker, M. R.; Schindler, C. S. Synthesis of Azetidines by Aza Paternò–Büchi Reactions. *Chem. Sci.* **2020**, *11* (29), 7553–7561.
- (14) Flores, D. M.; Neville, M. L.; Schmidt, V. A. Intermolecular 2 + 2 Imine-Olefin Photocycloadditions Enabled by Cu(I)-Alkene MLCT. *Nat. Commun.* **2022**, *13* (1), 2764.
- (15) Xu, K.; Fang, Y.; Yan, Z.; Zha, Z.; Wang, Z. A Highly Tunable Stereoselective Dimerization of Methyl Ketone: Efficient Synthesis of E- and Z-1,4-Enediones. *Org. Lett.* **2013**, *15* (9), 2148–2151.
- (16) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. Updating and Further Expanding GSK's Solvent Sustainability Guide. *Green Chem.* **2016**, *18* (13), 3879–3890.
- (17) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehadeh, S.; Dunn, P. J. CHEM21 Selection Guide of Classical- and Less Classical-Solvents. *Green Chem.* **2016**, *18* (1), 288–296.
- (18) Wiseman, L. R.; McTavish, D. Trandolapril. *Drugs* **1994**, *48* (1), 71–90.
- (19) Lahiri, S.; Dabral, V.; George, M. V. Thermal Addition of Dibenzoylacetylene to Cycloheptatriene and the Photo-Rearrangement of the Thermal Adduct. *Tetrahedron* **1978**, *34* (15), 2305–2314.
- (20) Barik, R.; Bhattacharyya, K.; Das, P. K.; George, M. V. Photochemical Transformations of 1-Imidazolyl-1,2-Dibenzoylalkenes. Steady-State and Laser Flash Photolysis Investigations. *J. Org. Chem.* **1986**, *51* (18), 3420–3428.
- (21) Staudinger, H. Zur Kenntniss der Ketene. Diphenylketen. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51–123.
- (22) Jiao, L.; Liang, Y.; Xu, J. Origin of the Relative Stereoselectivity of the β -Lactam Formation in the Staudinger Reaction. *J. Am. Chem. Soc.* **2006**, *128* (18), 6060–6069.

Recommended by ACS

Photoinduced Temperature-Regulated Selective Carbene C–H Insertion for the Synthesis of Functionalized Spiro- β -lactones and -lactams

Abdur Rouf Samim Mondal, Durga Prasad Hari, *et al.*

JUNE 09, 2023
ORGANIC LETTERS

READ 

Photo- or Electrochemical Cyclization of Dienes with Diselenides to Access Seleno-Benzo[*b*]azepines

Pengpeng Tan, Zhen Zhang, *et al.*

MAY 23, 2023
THE JOURNAL OF ORGANIC CHEMISTRY

READ 

Migration from Photochemistry to Electrochemistry for [2 + 2] Cycloaddition Reaction

Issa Yavari and Sina Shaabanzadeh

JUNE 08, 2023
THE JOURNAL OF ORGANIC CHEMISTRY

READ 

Chemodivergent Chalcogenation of Aryl Alkynoates or *N*-Arylpropynamides Using 9-Mesityl-10-Methylacridinium Perchlorate Photocatalyst

Ashis Mathuri, Prasenjit Mal, *et al.*

JULY 02, 2023
THE JOURNAL OF ORGANIC CHEMISTRY

READ 

Get More Suggestions >