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ORIGINAL PAPERS

Synthesis of 1*H*-isoindolin-1-ones via a simple photodecarboxylative addition of carboxylates to phthalimides and evaluation of their antibiotic activity

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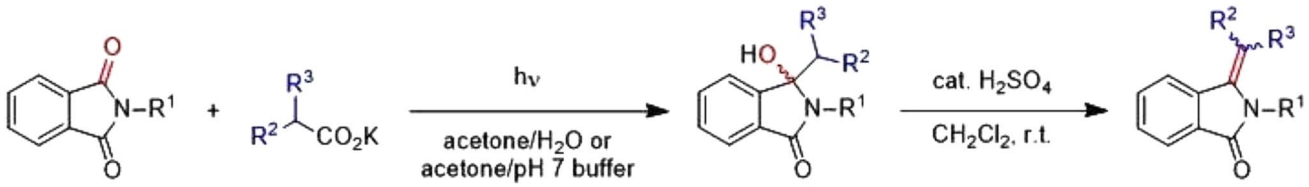
Abstract
A variety of 3-hydroxy-isoindolin-1-one derivatives were synthesized using the photodecarboxylative addition of carboxylates to phthalimide derivatives in aqueous media. Subsequent acid-catalyzed dehydration furnished 3-(alkyl and aryl) methyleneisoindolin-1-ones with variable *E*-diastereoselectivity in good to excellent overall yields. Noteworthy, the parent 3-phenylmethyleneisoindolin-1-one underwent isomerization and oxidative decomposition when exposed to light and air. Selected 3-hydroxy-isoindolin-1-one and 3-(alkyl and aryl)methyleneisoindolin-1-one derivatives showed moderate antibacterial activity that justifies future elaboration and study of these important bioactive scaffolds.

Graphical abstract



Keywords Photodecarboxylation · Phthalimides · Photo-induced electron transfer · Isoindolinones · Antibiotic activity

1 Introduction

The isoindolin-1-one scaffold (**I**) has gained considerable focus in synthetic organic chemistry due to its broad biological activity profile (Scheme 1) [1–5]. Among these, the *E*-phenylethylidene derivative AKS-186 (**II**) exhibited inhibition of thromboxane A_2 analog (U-46619)-induced vasoconstriction [6], while chlortalidone serves as a first-line medication for the treatment of high blood pressure [7]. Alkylated and benzylated 3-hydroxy-isoindolin-1-ones can be readily accessed through the photodecarboxylative addition of carboxylates to *N*-substituted phthalimides. This process has been developed as a versatile alternative to conventional alkylation reactions [8, 9]. In general, photodecarboxylations of carboxylic acids and their corresponding salts serve as an attractive source of alkyl radicals due to the easy availability, inexpensiveness, and stability of these feedstock materials [10–12], as well as the ability to scale up these reaction protocols [13–18]. Subsequent acid-catalyzed dehydration of the photoaddition products readily yields the important 3-alkyl and 3-arylmethylene-2,3-dihydro-1*H*-isoindolin-1-ones in high yields [19, 20].

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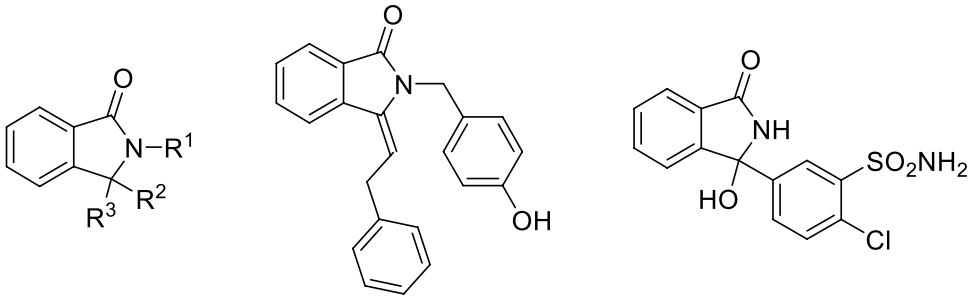
Scheme 1 The isoindol-1-one scaffold and representative bioactive examples



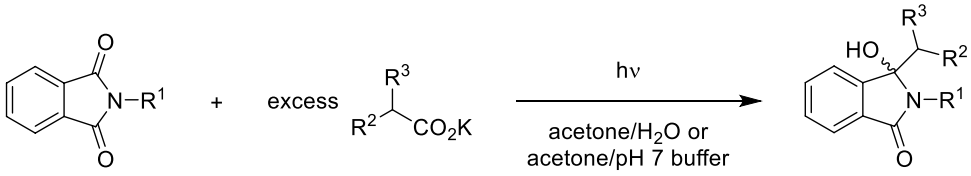
I **II** (*AKS-186*) **III** (*chlortalidone*)

2 Results and discussion

2.1 Photodecarboxylative addition reactions

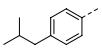
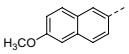
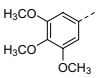
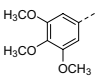
A series of readily accessible phthalimides **1a–g** were irradiated in the presence of three or ten equivalents of various potassium or sodium carboxylates **2a–m** (Scheme 2). The photoreactions were conducted in Pyrex vessels until TLC analysis indicted complete consumption of **1a–g**. In line with previous optimization studies [20, 21], two solvent systems were tested, either a 1:1 vol-% mixture of acetone and water (method **A**) or alternatively of acetone and pH 7 buffer solution (method **B**), respectively. No dramatic differences in yields or irradiation times were noted and method **A** was subsequently applied to all further experiments due to its simplicity. After irradiation with UV-B light ($\lambda = 300 \pm 25$ nm; 16 × 8 W) for 2–30 h, the addition products **3a–s** were obtained in isolated yields of 40–92% (Table 1). All photoproducts exhibited the characteristic singlet representative of the newly formed C–OH functionality at approximately 90–95 ppm in their ^{13}C-NMR spectra. In accordance with earlier observations [9, 21, 22], photodecarboxylative additions involving the simple alkyl carboxylates **2a–e** to *N*-methylphthalimide **1a** proceeded with lower efficiency, requiring prolonged irradiation times and large excess amounts of carboxylate (10 equivalents) to reach high conversions and acceptable yields of **3a–e** of 40–88% (entries 1–5). These inefficiencies were most likely caused by competitive 'simple' decarboxylations ($-CO_2^-$/-H exchange), *i.e.,* the formation of the respective volatile alkanes of **2a–e** [23, 24]. These 'simple' decarboxylation products have been identified in crude product mixtures before but are typically removed by evaporation or during purification [9, 25]. In solution, the methylated photoproduct **3a** was found to be sensitive toward spontaneous dehydration. In contrast, photodecarboxylative benzylations of arylacetates **2f–k** (3 equivalents) [26] to phthalimide **1a** proceeded rapidly and furnished the corresponding photoproducts **3f–k** in good to high yields of 53–92% (entries 6–17). Irradiations conducted using pH 7 buffer solution as co-solvent performed somewhat cleaner due to the avoidance of extreme pH conditions at higher conversion rates [27]. Despite their known photochemical activities [28, 29], the salts of the non-steroidal anti-inflammatory drugs ibuprofen (**2j**) and naproxen (**2k**) reacted readily and selectively. The presence of diastereomers for compounds **3h–l** was observed via NMR analysis, with varying diastereomeric excess (*d.e.*) ratios of 1:1 to 17:1 (entries 9–17). To expand the scope of novel products synthesized, six additional *N*-substituted phthalimide derivatives **1b-g** were investigated with photodecarboxylative benzylations involving **2f** proceeding as the most efficient [22, 30]. *N*-Isopropylphthalimide (**1b**) preferentially underwent benzylation to **3m** in a yield of 66% (entry 18), while the isomeric *N*-cyclopropylphthalimide (**1c**) solely reacted with the electron-deficient arylacetate **2m** after exhaustive irradiation for 19 h to **3n** in a respectable yield of 68% (entry 19). Competitive intramolecular Norrish reactions were not observed for either of the two phthalimide derivatives [31, 32]. Likewise, for the allylated and ester-containing phthalimides **1e–g**, no addition reactions to the corresponding *N*-sidechains were noted and selective photodecarboxylative additions to compounds **3p–s** operated instead (entries 21–24) [33, 34].

Scheme 2 Photodecarboxylative additions of **2a–m** to phthalimides **1a–g**



1a-g **2a-m** **3a-s**

Table 1 Product yields and experimental details for photodecarboxylative additions of **2a–m** to **1a–g**

Entry	**1**	**2**		Time/h (Method[a])	Conversion of **1**/%[b]	Yield of **3**/%
	R^1	R^2	R^3			
1	CH_3 (**a**)	H	H (**a**)	30 (**A**)	55	40 (**a**)
2	CH_3 (**a**)	CH_3	H (**b**)	20 (**A**)	100	49 (**b**)
3	CH_3 (**a**)	CH_3	CH_3 (**c**)	24 (**A**)	93	61 (**c**)
4	CH_3 (**a**)	$(CH_2)_2CH_3$	H (**d**)	24 (**A**)	98	88 (**d**)
5	CH_3 (**a**)	$(CH_2)_5CH_3$	H (**e**)	22 (**A**)	92	42 (**e**)
6	CH_3 (**a**)	Ph	H (**f**)	7 (**A**)	100	62 (**f**)
7				3 (**B**)	83	79 (**f**)
8	CH_3 (**a**)		H (**g**)	7 (**A**)	88	53 (**g**)
9	CH_3 (**a**)	Ph	CH_3 (**h**)	4 (**A**)	100	73 (3:2[c], **h**)
10				3 (**B**)	95	83 (17:1[c], **h**)
11	CH_3 (**a**)	Ph	Et (**i**)	3 (**A**)	100	74 (1:1[c], **i**)
12				3 (**B**)	93	78 (3:2[c], **i**)
13	CH_3 (**a**)		CH_3 (**j**)[d]	3 (**A**)	100	74 (3:2[c], **j**)
14				5 (**B**)	96	92 (11:9[c], **j**)
15	CH_3 (**a**)		CH_3 (**k**)	5 (**A**)	100	89 (9:1[c], **k**)
16	CH_3 (**a**)	Ph	CH_3O (**l**)	3 (**A**)	100	83 (3:2[c], **l**)
17				3 (**B**)	98	89 (11:9[c], **l**)
18	^{i}Pr (**b**)	Ph	H (**f**)	2 (**A**)	95	66 (**m**)
19	^{c}Pr (**c**)		H (**m**)	19 (**A**)	100	68 (**n**)
20	p-TolCH_2 (**d**)	Ph	H (**f**)	3 (**A**)	100	89 (**o**)
21	CH_2=$CHCH_2$ (**e**)	Ph	H (**f**)	6 (**A**)	100	51 (**p**)
22	CH_2=$CHCH_2$ (**e**)		H (**m**)	20 (**A**)	100	53 (**q**)
23	$CH_3O_2CCH_2$ (**f**)	Ph	H (**f**)	3 (**A**)	100	76 (**r**)
24	EtO_2CCH_2 (**g**)	Ph	H (**f**)	2 (**A**)	93	51 (**s**)

[a]Conditions: 1:1 vol-% mixtures of acetone–water (Method **A**) or acetone and pH 7 buffer (Method **B**) of **1** (15 mM) and **2** (30–150 mM) were irradiated with UV-B light ($\lambda = 300 \pm 25$ nm) in a Pyrex Schlenk flask under N_2-purging

[b]Conversion determined by integration of baseline separated signals in the ^{1}H-NMR spectrum of the crude reaction mixture (±5%)

[c]Diastereomeric excess (*d.e.*) determined by integration of baseline separated signals in the ^{1}H-NMR spectrum of the isolated product (±5%)

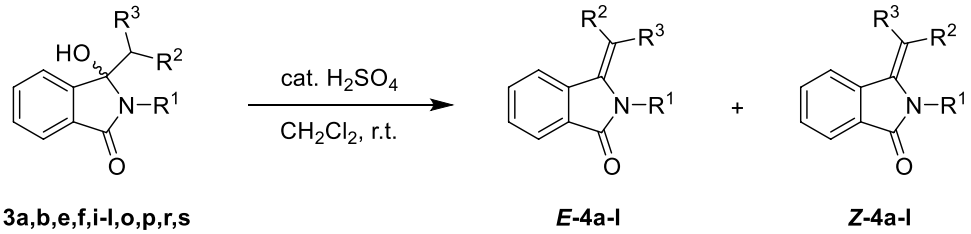
[d]Used as a sodium salt

The mechanism of the photodecarboxylative addition of carboxylates to phthalimides through triplet sensitization and subsequent photoinduced electron transfer (PET) is well understood and has been described in detail elsewhere [35–37]. With the exception of the trimethoxyphenyl acetate **2f**, the carboxylate group acts as an electron donor to generate an unstable carboxy radical. In case of **2f**, the electron-rich aryl moiety functions as an electron donor instead [38]. In both cases, successive decarboxylation, protonation, and C–C bond formation yield the observed addition products **3a–s**.

2.2 Acid-catalyzed dehydrations and stability testing

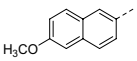
Several of the photoproducts **3** were submitted to acid-catalyzed dehydration conditions to yield the corresponding 3-alkyl and 3-arylmethylene-1*H*-isoindolin-1-ones **4a–l** (Scheme 3) [39–41]. This was conveniently achieved by stirring a solution of the respected 3-hydroxy-isoindolin-1-one in dichloromethane in the presence of catalytic amounts of concentrated sulfuric acid (Table 2) [19, 20]. This procedure furnished the desired dehydration products **4a–l** in good

Scheme 3 Acid-catalyzed dehydration of selected 3-hydroxyisoindolin-1-ones **3** to 3-alkyl and 3-arylmethylene-1*H*-isoindolin-1-ones **4a–l**



3a,b,e,f,i-l,o,p,r,s ***E*-4a-l** ***Z*-4a-l**

Table 2 Product yields and experimental details for acid-catalyzed dehydrations to **4a–l**

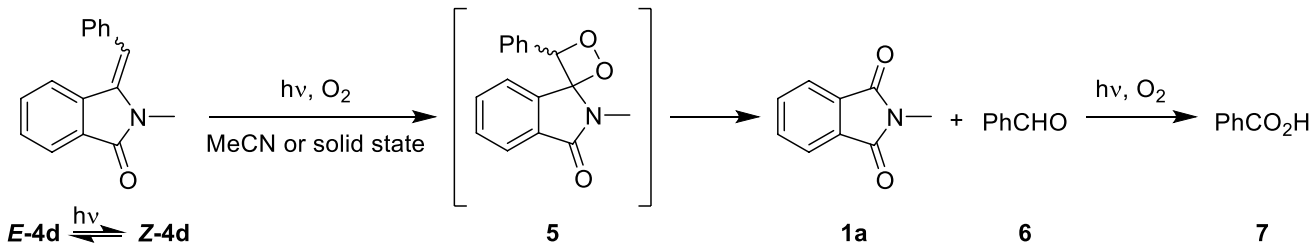
Entry	**3**			**4**	
	R^1	R^2	R^3	*E/Z*-ratio[a]	Yield/%
1	CH_3	H	H (**a**)	–	97 (**a**)
2	CH_3	CH_3	H (**b**)	8:1	92 (**b**)
3	CH_3	$(CH_2)_5CH_3$	H (**e**)	9:1	94 (**c**)
4	CH_3	Ph	H (**f**)	9:1	96 (**d**)
5	CH_3	Ph	Et (**i**)	1:1	74 (**e**)
6	CH_3		CH_3 (**j**)	1:1	97 (**f**)
7	CH_3		CH_3 (**k**)	1:1	98 (**g**)
8	CH_3	Ph	CH_3O (**l**)	1:2	72 (**h**)
9	p-TolCH_2	Ph	H (**o**)	> 10:1	99 (**i**)
10	CH_2=$CHCH_2$	Ph	H (**p**)	9:1	77 (**j**)
11	$CH_3O_2CCH_2$	Ph	H (**r**)	5:1	64 (**k**)
12	EtO_2CCH_2	Ph	H (**s**)	4:1	60 (**l**)

[a]Determined by integration of baseline separated signals in the ^{1}H-NMR spectrum of the isolated product (±5%)

to excellent yields of 60–99%. Except for **4a** (entry 1), all dehydration products produced mixtures of *E*- and *Z*-isomers and their diastereomeric ratios varied depending on the substituents (entries 2–12). The diastereoisomers of **4b–l** were assigned by comparison with literature data and ^{1}H-NMR spectroscopic analyses, respectively. In contrast to their corresponding *E*-isomers, the olefinic protons of the *Z*-isomers of **4** were shifted downfield by the adjacent isoindolin-1-one ring [35, 42].

In agreement with theoretical calculations by Kise et al. [43] and Li and Janesko [44], all trisubstituted arylmethylene-1*H*-isoindolin-1-ones **4b–d** and **i–l** predominantly gave the thermodynamically favored *E*-isomer as the major product. Low to no diastereoselectivities were found for the tetrasubstituted dehydration products **4e–h** instead. As previously noted by other groups [41, 43], the dehydration products **4** were sensitive toward spontaneous degradation in the solid state or in solution when exposed to air and visible light. The stability of the parent 3-phenylmethyleneisoindolin-1-one ***E*-4d** was thus investigated under a variety of environmental conditions (Scheme 4; Table 3). In the absence of light in the solid state or in acetonitrile solution, no reaction was observed despite the presence of air (entries 1 and 2). Irradiations in acetonitrile with UV-B light solely induced *E/Z*-photoisomerization into an approx. 1:1 mixture (entries 3 and 4) as reported in the literature [21]. Importantly, exposure of solid ***E*-4d** to ambient light in air caused complete degradation, with *N*-methylphthalimide **1a**, benzaldehyde **6** and benzoic acid **7** as the main products detected (entry 5), as confirmed by spiking experiments. The potential presence of the isomeric dioxetanes **5** was suggested by characteristic singlet signals in the required 1:3 ratios at 5.19 and 5.28 ppm for their methine C–H moieties [45, 46] and at 3.10 and 3.11 ppm for their N–CH_3 groups, respectively. Since the oxidative cleavage to **1a** and **6** is believed to operate via a [2 + 2]-cycloaddition of singlet oxygen ($^1O_2$) [43, 47], a solution of ***E*-4d** and catalytic amounts of rose bengal in acetonitrile was irradiated with visible light while being purged with oxygen. After 5 h, a conversion of approximately 70% was observed, with photoisomerization and oxidative cleavage operating in parallel (entry 6).

To prevent these degradation processes, the dehydration products were stored under an inert gas atmosphere (Ar or N_2) and in amber vials. Noteworthy, these sparsely reported



***E*-4d ⇌ *Z*-4d** **5** **1a** **6** **7**

Scheme 4 Proposed oxidative decomposition mechanism of ***E*-4d**

Table 3 Stability test conditions and observation conducted with ***E*-4d**

Entry	Conditions	Observations[a]
1	Standing in the dark in the solid state while exposed to air for 7 days	No changes noted
2	Standing in the dark in acetonitrile while exposed to air for 24 h	No changes noted
3	Exposure of a degassed acetonitrile solution to UV-B light for 24 h	Photoisomerization to an approx. 1:1 mixture of ***E*/*Z*-4d**
4	Exposure of an aerated acetonitrile solution to UV-B light for 24 h	Photoisomerization to an approx. 1:1 mixture of ***E*/*Z*-4d**
5	Exposure to ambient light and air in the solid state for 7 days	Presumed formation of **5** (12%) and decomposition to **1a** (62%), **6** (3%[b]) and **7** (23%)
6	Exposure to visible light in acetonitrile solution with catalytic amounts of rose bengal while purging with oxygen for 5 h	Photoisomerization to ***Z*-4e** (47%), presumed formation of **5** (3%) and oxidative decomposition to **1a** (14%) and **6** (7%[b])

[a]Determined by integration of baseline separated signals in the ^{1}H-NMR spectrum (±5%)

[b]Evaporation losses of additionally formed **6** cannot be excluded

decomposition pathways pose a significant challenge to the usability of 3-methylene-1*H*-isoindolin-1-one derivatives and must be considered when generating, analyzing, or utilizing these compounds.

2.3 Antimicrobial activity testing

Due to the known antimicrobial activity of structurally related isoindolin-1-ones [1–5, 48], a total of eight of the 3-hydroxy-isoindolin-1-one photoadducts, *i.e.*, **3c**, **f**, **i**, **j**, **l**, **m**, **o** and **p**, and five of the methylene-1*H*-isoindolin-1-one dehydration products, *i.e.*, **4c–e**, **h** and **i**, synthesized in this study were chosen for antibiotic activity screening. The additional hydroxy group in **3** may offer beneficial pharmacological properties [49, 50]. The disk diffusion method versus suitable control antibiotics was chosen using three different bacteria (Table 4) [51, 52]: the Gram-positive *Staphylococcus aureus* and the Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*, respectively. Compounds **4c**, **d** and **h** inhibited growth of both, *S. aureus* and *Ps. aeruginosa*, but were inactive against *E. coli* at the tested doses (entries 9, 11 and 14). Activities against *S. aureus* were noted for the photoproducts **3f** and **l** (entries 2 and 5), while compound **3j** was moderately active against *Ps. aeruginosa* (entry 4). Inhibition of *E. coli* was only observed for compounds **3m** and **3o** at high concentrations (entries 6 and 7), with the later also showing low activity against *S. aureus*.

These results show the potential of the isoindolin-1-one scaffold to inhibit bacterial growth. However, more research needs to be conducted to gain a deeper understanding of their efficacy and suitability in this utilization.

Table 4 Antimicrobial activity of selected photoaddition and dehydration products against *S. aureus*, *E. coli* and *P. aeruginosa*

Entry	Compound	*S. aureus*[a]	*E. coli*[a]	*P. aeruginosa*[a]
1	**3c**	Inactive (59)	Inactive (59)	–
2	**3f**	Weakly active[b] (444)	Inactive (444)	Inactive (444)
3	**3i**	Inactive (190)	Inactive (48)	Inactive (190)
4	**3j**	Inactive (180)	Inactive (45)	Moderately active[b] (180)
5	**3l**	Weakly active (192)	Inactive (48)	Inactive (192)
6	**3m**	Inactive (128)	Moderately active (128)	Inactive (128)
7	**3o**	Weakly active[b] (464)	Moderately active (464)	Inactive (464)
8	**3p**	Inactive (198)	Inactive (50)	Inactive (198)
9	**4c**	Moderately active (236)	Inactive (59)	Weakly active (236)
10		Weakly active (59)		
11	**4d**	Weakly active (208)	Inactive (52)	Moderately active[b] (208)
12		Inactive (52)		
13	**4e**	Inactive (194)	Inactive (49)	Inactive (194)
14	**4h**	Weakly active (232)	Inactive (58)	Moderately active[b] (232)
15		Inactive (58)		
16	**4i**	Inactive (232)	Inactive (232)	Inactive (232)

[a]Amounts on disk (in µg) in 20 µl of ultrapure acetone given in brackets

[b]Regrown colony formation units (CFUs) were present within the inhibition zones after 48 h

3 Conclusions

In conclusion, a library of diversely substituted 3-hydroxy-isoindolin-1-ones was generated via photodecarboxylative addition of readily available carboxylates to *N*-substituted phthalimides. Subsequent dehydration under mild conditions furnished a series of novel 3-(alkyl and aryl)methylene-2,3-dihydro-1*H*-isoindolin-1-ones. The simple protocols make this tandem-process an attractive application for telescoping under continuous flow conditions [53–55]. Antibiotic screening of a variety of compounds synthesized revealed several active hit compounds, justifying further medicinal chemistry studies. However, the somewhat limited stability of 3-(alkyl and aryl)methylene-2,3-dihydro-1*H*-isoindolin-1-ones demands special care when dealing with these compounds.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43630-024-00600-y.

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Data availability Original data are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest There are no conflicts of interest to declare.

References

1. Lan, C. B., & Auclair, K. (2024). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): an organocatalyst for rapid access to 3-hydroxy-isoindolin-1-ones. *European Journal of Organic Chemistry, 27*, e202400071.
2. Jassem, A. M., & Dhumad, A. M. (2020). Microwave-assisted green synthesis, antimicrobial activity, and drug-likeness of novel isoindolinone derivatives. *Monatshefte fuer Chemie, 151*, 1433–1442.
3. Li, H.-J., Zhang, Y.-Q., & Tang, L.-F. (2015). A simple and efficient synthesis of isoindolinone derivatives based on reaction of ortho-lithiated aromatic imines with CO. *Tetrahedron, 71*, 7681–7686.
4. Lamblin, M., Couture, A., Deniau, E., & Grandclaudon, P. (2007). A concise first total synthesis of narceine imide. *Organic & Biomolecular Chemistry, 5*, 1466–1471.
5. Breytenbach, J. C., van Dyk, S., van den Heever, I., Allin, S. M., Hodkinson, C. C., Northfield, C. J., & Page, M. I. (2000). Synthesis and antimicrobial activity of some isoindolin-1-ones derivatives. *Bioorganic & Medicinal Chemistry Letters, 10*, 1629–1631.
6. Kato, Y., Takemoto, M., & Achiwa, K. (1999). Prostanoids and related compounds. VII. Synthesis and inhibitory activity of 1-isoindolinone derivatives possessing inhibitory activity against thromboxane A_2 analog (U-46619)-induced vasoconstriction. *Chemical & Pharmaceutical Bulletin, 47*, 529–535.
7. Dineva, S., Uzunova, K., Pavlova, V., Fikipova, E., Kalinov, K., & Vekov, T. (2019). Comparative efficacy and safety of chlorthalidone and hydrochlorothiazide-meta-analysis. *Journal of Human Hypertension, 33*, 766–774.
8. Mumtaz, S., Robertson, M. J., & Oelgemöller, M. (2018). Recent advances in photodecarboxylations involving phthalimides. *Australian Journal of Chemistry, 71*, 634–648.
9. Oelgemöller, M., Cygon, P., Lex, J., & Griesbeck, A. G. (2003). The photodecarboxylative addition of carboxylates to phthalimides: Scope and limitations. *Heterocycles, 59*, 669–684.
10. Yoshimi, Y. (2020). Recent applications of photoinduced decarboxylative radical reactions catalyzed by photoredox catalysts. *Photochemistry, 49*, 354–368.
11. Schwarz, J., & König, B. (2018). Decarboxylative reactions with and without light – a comparison. *Green Chemistry, 20*, 323–361.
12. Budac, D., & Wan, P. (1992). Photodecarboxylation: Mechanism and synthetic utility. *Journal of Photochemistry and Photobiology A: Chemistry, 67*, 135–166.
13. Graham, M. A., Noonan, G., Cherryman, J. H., Douglas, J. J., Gonzalez, M., Jackson, L. V., Leslie, K., Liu, Z.-Q., McKinney, D., Munday, R. H., Parsons, C. D., Whittaker, D. T. E., Zhang, E.-X., & Zhang, J.-W. (2021). Development and proof of concept for a large-scale photoredox additive-free Minisci reaction. *Organic Process Research & Development, 25*, 57–67.
14. Kortmann, F. A., Hermsen, P., & De Vries, A. H. M. (2021). Photoinduced decarboxylative borylation: Scaling visible light photochemistry. *Chimica Oggi – Chemistry Today, 39*, 28–31.
15. DeLaney, E. N., Lee, D. S., Elliott, L. D., Jin, J., Booker-Milburn, K. I., Poliakoff, M., & George, M. W. (2017). A laboratory-scale annular continuous flow reactor for UV photochemistry using excimer lamps for discrete wavelength excitation and its use in a wavelength study of a photodecarboxlyative cyclisation. *Green Chemistry, 19*, 1431–1438.
16. Oelgemöller, M. (2014). Green photochemical processes and technologies for research & development, scale-up and chemical production. *Journal of the Chinese Chemical Society, 61*, 743–748.
17. Griesbeck, A. G., Maptue, N., Bondock, S., & Oelgemöller, M. (2003). The excimer radiation system: A powerful tool for preparative organic photochemistry. A technical note. *Photochemical & Photobiological Sciences, 2*, 450–451.
18. Griesbeck, A. G., Kramer, W., & Oelgemöller, M. (1999). Photoinduced decarboxylation reactions. Radical chemistry in water. *Green Chemistry, 1*, 205–207.
19. Anamimoghadam, O., Mumtaz, S., Nietsch, A., Saya, G., Motti, C. A., Wang, J., Junk, P. C., Qureshi, A. M., & Oelgemöller, M. (2017). The photodecarboxylative addition of carboxylates to phthalimides as a key-step in the synthesis of biologically active 3-arylmethylene-2,3-dihydro-1H-isoindolin-1-ones. *Beilstein Journal of Organic Chemistry, 13*, 2833–2841.
20. Hatoum, F., Engler, J., Zelmer, C., Wißen, J., Motti, C. A., Lex, J., & Oelgemöller, M. (2012). Photodecarboxylative addition of

carboxylates to phthalimides: A concise access to biologically active 3-(alkyl and aryl)methylene-1H-isoindolin-1-ones. *Tetrahedron Letters, 53*, 5573–5577.
21. Belluau, V., Noeureuil, P., Ratzke, E., Skvortsov, A., Gallagher, S., Motti, C. A., & Oelgemöller, M. (2010). Photodecarboxylative benzylations of phthalimide in pH 7 buffer: A simple access to 3-arylmethyleneisoindolin-1-ones. *Tetrahedron Letters, 51*, 4738–4741.
22. Griesbeck, A. G., Warzecha, K.-D., Neudörfl, J. M., & Görner, H. (2004). Photodecarboxylative benzylation of N-alkylphthalimides: A concise route to the aristolactam skeleton. *Synlett, 13*, 2347–2350.
23. Duong, H. T., Wu, Y., Sutor, A., Burek, B. O., Hollmann, F., & Bloh, J. Z. (2021). Intensification of photobiocatalytic decarboxylation of fatty acids for the production of biodiesel. *Chemsuschem, 14*, 1053–1056.
24. Yokoi, H., Nakano, T., Fujita, W., Ishiguro, K., & Sawaki, Y. (1998). In-cage formation of carbanions in photoinduced electron-transfer reaction of carboxylate ions. *Journal of the American Chemical Society, 120*, 12453–12458.
25. Hatoum, F., Gallagher, S., & Oelgemöller, M. (2009). Photodecarboxylative additions of phenoxyacetates to N-methylphthalimide. *Tetrahedron Letters, 50*, 6593–6596.
26. Yang, C., Sheng, X., Zhang, L., Yu, J., & Huang, D. (2020). Arylacetic acids in organic synthesis. *Asian Journal of Organic Chemistry, 9*, 23–41.
27. Griesbeck, A. G., Heinrich, T., Oelgemöller, M., Molis, A., & Heidtmann, A. (2002). Synthesis of cyclic peptides by photochemical decarboxylation of N-phthaloyl peptides in aqueous solution. *Helvetica Chimica Acta, 85*, 4561–4578.
28. Hua, L. F., Yao, K., Lv, V. Y., Liu, G. G., Chen, P., Huang, H. P., & Kang, Y. P. (2015). Photodegradation of ibuprofen under UV-Vis irradiation: Mechanism and toxicity of photolysis products. *Bulletin of Environment Contamination and Toxicology, 94*, 479–483.
29. Arany, E., Szabó, R. K., Apáti, L., Alapi, T., Ilisz, I., Mazellier, P., Dombi, A., & Gajda-Schrantz, K. (2013). Degradation of naproxen by UV, VUV photolysis and their combination. *Journal of Hazardous Materials, 262*, 151–157.
30. Hatoum, F., Gallagher, S., Baragwanath, L., Lex, J., & Oelgemöller, M. (2009). Photodecarboxylative benzylations of phthalimides. *Tetrahedron Letters, 50*, 6335–6338.
31. Kanaoka, Y., Migita, Y., Koyama, K., Sato, Y., Nakai, H., & Mizoguchi, T. (1973). Photochemistry of the phthalimide system. IV. Photocyclization of N-alkylphthalimides benzazepinone lactams: Unusual two-fold Norrish type II reactions. *Tetrahedron Letters, 14*, 1193–1196.
32. Kanaoka, Y., Koyama, K., Flippen, J. L., Karle, I. L., & Witkop, B. (1974). Photocyclization of N-alicyclic phthalimides. Synthesis of multicyclic benzazepine systems. *Journal of the American Chemical Society, 96*, 4719–4721.
33. Shiraishi, Y., Tsukamoto, D., & Hirai, T. (2008). Highly efficient methyl ketone synthesis by water-assisted C-C coupling between olefins and photoactivated acetone. *Organic Letters, 10*, 3117–3120.
34. Pigeon, P., Othman, M., & Decroix, B. (2001). Thieno[2',3':5,6] azepino[2,1-a]isoindolones from hydroxylactam-alcohols via N-acyliminium ion olefin cyclization. *Journal of Heterocyclic Chemistry, 38*, 35–39.
35. Griesbeck, A. G., Neudörfel, J.-M., Goldfuss, B., & Molitor, S. (2017). Synthesis of 3-benzylated isoindolinones by photoredox decarboxylation of arylacetates in the presence of N-benzylphthalimide: Conductivity as a kinetic tool. *ChemPhotoChem, 1*, 355–362.
36. Mandić, L., Sohora, M., Mihaljević, B., Biczók, L., & Basarić, N. (2021). The effect of the rate of photoinduced electron transfer on the photodecarboxylation efficiency in phthalimide photochemistry. *Journal of Photochemistry and Photobiology A: Chemistry, 408*, 113109.
37. Görner, H., Oelgemöller, M., & Griesbeck, A. G. (2002). Photodecarboxylation study of carboxy-substituted N-alkylphthalimides in aqueous solution: Time resolved UV-Vis spectroscopy and conductometry. *Journal of Physical Chemistry A, 106*, 1458–1464.
38. Warzecha, K.-D., Görner, H., & Griesbeck, A. G. (2006). Photoinduced decarboxylative benzylation of phthalimide triplets with phenyl acetates: A mechanistic study. *Journal of Physical Chemistry A, 110*, 3356–3363.
39. Topolovčan, N., Duplić, F., & Gredičak, M. (2021). Influence of N-substitution in 3-alkyl-3-hydroxyisoindolin-1-ones on the stereoselectivity of Broensted acid-catalyzed synthesis of 3-methyleneisoindolin-1-ones. *European Journal of Organic Chemistry, 2021*, 3920–3924.
40. Scartoni, V., & Tognetti, T. (1984). 2-Phenylphthalimidine derivatives. A probable formation mechanism of adducts from 3-benzylidenephthalide and aniline. *Journal of Heterocyclic Chemistry, 21*, 1499–1503.
41. Heidenbluth, K., Tönjes, H., & Scheffler, R. (1965). Zur Grignard-Reaktion mit Phthalimiden. *Journal für Praktische Chemie, 30*, 204–217.
42. Ang, W. S., & Halton, B. (1971). The configuration of alkylidenephthalimidine derivatives. *Australian Journal of Chemistry, 24*, 851–856.
43. Kise, N., Kawano, Y., & Sakurai, T. (2013). Reductive coupling of phthalimides with ketones and aldehydes by low-valent titanium: One-pot synthesis of alkylideneisoindolin-1-ones. *Journal of Organic Chemistry, 78*, 12453–12459.
44. Li, L., & Janesko, B. G. (2016). 3-Methyleneisoindolin-1-one assembly via base- and CuI/L-proline-catalyzed domino reaction: Mechanism of regioselective anionic cyclization. *Journal of Organic Chemistry, 81*, 10802–10808.
45. Foote, C. S., & Lin, J.W.-P. (1968). Chemistry of singlet oxygen. VI. Photooxygenation of enamines: Evidence for an intermediate. *Tetrahedron Letters, 9*, 3267–3270.
46. Foote, C. S., Dzakpasu, A. A., & Lin, J.W.-P. (1975). Chemistry of singlet oxygen. XX. Mechanism of the sensitized photooxidation of enamines. *Tetrahedron Letters, 14*, 1247–1250.
47. Li, L., Cai, S., Chen, J., Zhao, Y., & Wang, D. Z. (2014). Visible light induced photocatalytic conversion of enamines into amides. *Synlett, 25*, 1626–1628.
48. Ibbotson, L. T., Christensen, K. E., Genov, M., Pretsch, A., Pretsch, D., & Moloney, M. G. (2023). Tricyclic fused lactams by Mukaiyama cyclisation of phthalimides and evaluation of their biological activity. *Antibiotics, 12*, 9.
49. Cramer, J., Sager, C. P., & Beat, E. (2019). Hydroxyl groups in synthetic and natural-product-derived therapeutics: A perspective on a common functional group. *Journal of Medicinal Chemistry, 62*, 8915–8930.
50. Stella, V. J., Charman, W. N. A., & Naringrekar, V. H. (1985). Prodrugs. *Drugs, 29*, 455–473.
51. Cushnie, T. P. T., Cushnie, B., Echeverría, J., Fowsantear, W., Thammawat, S., Dodgson, J. L. A., Law, S., & Clow, S. M. (2020). Bioprospecting for antibacterial drugs: A multidisciplinary perspective on natural product source material, bioassay selection and avoidable pitfalls. *Pharm Research, 37*, 125.
52. Miles, W. H., & Smiley, P. M. (2002). Modeling the drug discovery process: The isolation and biological testing of eugenol from clove oil. *Journal of Chemical Education, 79*, 90.

53. Otake, Y., Nakamura, H., & Fuse, S. (2018). Recent advances in the integrated micro-flow synthesis containing photochemical reactions. *Tetrahedron Letters, 59*, 1691–1697.
54. Mumtaz, S., Robertson, M. J., & Oelgemöller, M. (2019). Continuous flow photochemical and thermal multi-step synthesis of bioactive 3-arylmethylene-2,3-dihydro-1H-isoindolin-1-ones. *Molecules, 24*, 4527.
55. Josland, S., Mumtaz, S., & Oelgemöller, M. (2016). Photodecarboxylations in an advanced meso-scale continuous-flow photoreactor. *Chemical Engineering and Technology, 39*, 81–87.