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Electron Donor-Acceptor Complex-Assisted Photochemical Conversion of *O*-2-Nitrobenzyl Protected Hydroxamates to Amides

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The hydroxamic acid functionality is present in various medicinal agents and has attracted special interest for synthetic transformations in both organic and medicinal chemistry. The N–O bond cleavage of hydroxamic acid derivatives provides an interesting transformation for the generation of various products. We demonstrate, herein, that *O*-benzyl-type protected hydroxamic acids may undergo photochemical N–O bond cleavage, in the presence or absence of a catalyst, leading to amides. Although some *O*-benzyl protected aromatic hydroxamates may be photochemically converted to amides in the presence of a base and anthracene as the catalyst, employing *O*-2-nitrobenzyl group allowed the smooth conversion of both aliphatic and aromatic hydroxamates to primary or secondary amides in good to excellent yields in the presence of an amine, bypassing the need of a catalyst. DFT and UV-Vis studies supported the effective generation of an electron donor-acceptor (EDA) complex between *O*-2-nitrobenzyl hydroxamates and amines, which enabled the successful product formation under these photochemical conditions. An extensive substrate scope was demonstrated, showcasing that both aliphatic and aromatic hydroxamates are compatible with this protocol, affording a wide variety of primary and secondary amides.

Introduction

Hydroxamic acids, also known as *N*-hydroxy amides, have attracted great interest, since they possess interesting properties and find widespread applications in both Organic and Medicinal Chemistry.[1] Some of them, namely vorinostat, belinostat and panobinostat, have been approved for clinical use against primary cutaneous T-cell lymphoma, peripheral T-cell lymphoma and multiple myeloma, respectively.[2] The hydroxamic acid functionality exhibits distinct reactivity and may undergo various organic transformations.[3] In general, the N–O bond is a weaker bond, in comparison to a C–X (X=C, N, O) bond, and thus, compounds containing the N–O functionality may be cleaved under catalytic conditions, using either a transition-metal catalyst or a photocatalyst. Hence, the reductive N–O bond cleavage of hydroxamic acids and their derivatives has been reported to lead to the formation of primary amides (Scheme 1, **A**). In 1993, the $TiCl_3$-mediated conversion of *O*-methyl hydroxamates to primary amides at ambient to elevated temperature was described.[4] The use of 2 equiv. of $TiCl_3$ were required for the conversion to products. Later, the reduction of *N*-alkoxyamides to primary amides was accomplished by the treatment with Li in the presence of DTBB at −78 °C, where 8 equiv. of Li were necessary.[5] Recently, the reductive cleavage of the N–O bond of *N*-alkoxyamides to amides mediated by elemental sulfur-DABCO at 80 °C has been described.[6] Moreover, the N–O bond cleavage of N–OR (R=H, alkyl, or acyl) substituted amides was demonstrated by a ruthenium(II)-catalyzed reductive approach at 100 °C.[7] Additionally, Pace and coworkers reported a C1-installation within a N–O bond for the homologation of Weinreb amides to acyclic *N*-acyl-*N*,*O*-acetals via N–O heterolysis.[8]

In recent years, a revolutionary wave has given prominence to organic photochemistry, establishing photochemical methods as a powerful tool of synthetic organic chemistry, avoiding metal catalysts and employing mild reaction conditions, thus offering the advantage of green character.[9] Going along with current trends, the photochemical cleavage of N–O bond of oximes has been investigated in recent years,[10] finding some attractive applications.[11] However, the photochemical N–O bond cleavage of hydroxamates is conspicuously unexplored. Recently, during the studies of a photocaged panobinostat

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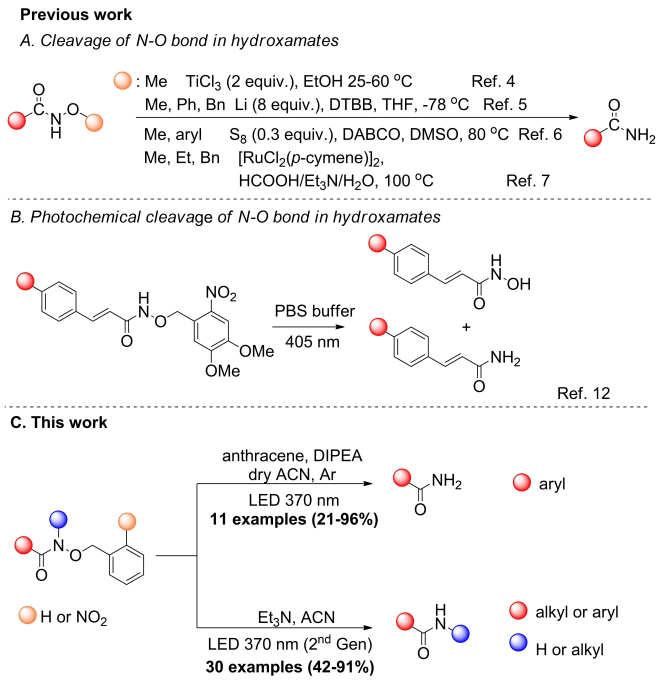


Scheme 1. Literature methods for the conversion of *O*-protected hydroxamates to amides and this work.

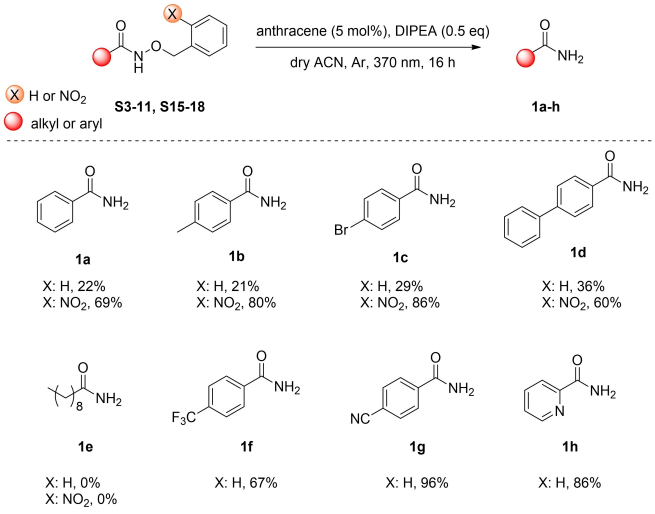
analogue, Troelsen *et al.* reported an unexpected partial formation of the corresponding primary amide from the protected hydroxamic acid (Scheme 1, B).[12] The formation of the amide byproduct of panobinostat suggests that the relatively weak N–O bond of the hydroxamic acid may be cleaved via an alternative photo-induced pathway. Gilmour demonstrated a photoorganocatalytic protocol for the N–O bond cleavage of Weinreb amides, employing either anthracene or 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[13] Most recently, a metal-organic bichromophore was demonstrated to transform Weinreb amides to amides under irradiation at 447 nm.[14]

Having a long interest in photochemical methodologies,[15] the aim of the present work was to investigate the photochemical cleavage of the N–O bond of benzyl-type *O*-protected hydroxamates. During the course of our study, we observed that *O*-2-nitrobenzyl hydroxamates may form an electron donor-acceptor (EDA) complex with amines, such as triethylamine (Et_3N) or *N,N*-diisopropylethylamine (DIPEA). In this work, we present a catalyst-free EDA-assisted photochemical method for the conversion of *O*-2-nitrobenzyl hydroxamates to primary and secondary amides in good to excellent yields (Scheme 1, C).

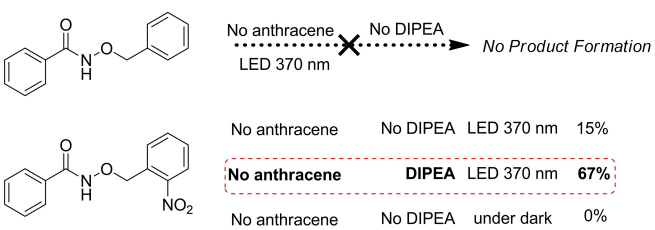
Results and Discussion

The benzyl group is a common group for the *O*-protection of hydroxamates to *O*-benzyl hydroxamates, which find wide use as intermediates for synthetic purposes involving hydroxamates. Inspired by the pioneer work of Gilmour on the photochemical conversion of Weinreb amides to methyl amides,[13] we started our study by exploring the conversion of a set of *O*-benzyl hydroxamates, following the conditions described in that work. More precisely, we employed 5 mol% anthracene as the catalyst in the presence of DIPEA (0.5 equiv.) in dry acetonitrile (ACN) under irradiation at 370 nm. These initial results are summarized in Scheme 2. *O*-Benzyl hydroxamates of benzoic, 4-methylbenzoic, 4-bromobenzoic or 4-phenylbenzoic acid were converted to amides **1a–d** in low yields (21–36%), while that of decanoic acid did not provide the desired product. However, some other hydroxamates of aromatic acids were converted to primary amides **1f–h** in high to excellent yields (67–96%) under these conditions. Then, we decided to replace the benzyl group by the 2-nitrobenzyl one, which in literature has been used as a photoremovable group.[16] Under the described conditions, the corresponding 2-nitrobenzyl aromatic hydroxamates afforded amides **1a–d** in high yields (60–86%). However, again an aliphatic substrate did not afford amide **1e**.

Using *O*-benzyl and *O*-2-nitrobenzyl hydroxamates of benzoic acid for control experiments, we observed that, under irradiation at 370 nm, in the absence of anthracene and DIPEA, the benzyl substrate remained intact (Scheme 3), while the 2-nitrobenzyl substrate afforded the primary amide in very low yield (15%), due to undesirable fragmentation to various non-separable byproducts. However, in the absence of anthracene and in the presence of DIPEA, the 2-nitrobenzyl substrate provided the amide in high yield (67%), indicating a clear role



Scheme 2. Photocatalytic conversion of *O*-benzyl-type protected hydroxamates to primary amides.



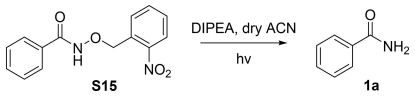
Scheme 3. Control experiments.

of the amine additive (Scheme 3). The 2-nitrobenzyl substrate also remained intact in the absence of anthracene, DIPEA and light irradiation, establishing the photocatalytic nature of this protocol.

To understand the role of the amine additive and the light source, we undertook a study exploring a range of amines and LED lamps. The results are summarized in Tables 1 and 2. Among the light sources utilized (Table 1), LED 370 nm 2nd gen (a second-generation lamp providing increased photon flux) afforded the highest yield (Table 1, entry 2). Although a number of common organic bases afforded the desired product (Table 2), triethylamine afforded the highest yield (Table 2, entry 2), followed by *N*-Me-pyrrolidine (Table 2, entry 3). Satisfactory reaction yields with more hindered amines confirmed the reaction's efficacy across different types of amine components. Moreover, the use of an inorganic base (K_2CO_3) also led to the desired product, albeit in lower yield (Table 2, entry 9). Adding water in the solvent system to fully solubilize K_2CO_3 led to inferior results (Table 2, entry 10).

Nitroarenes have recently attracted a renewed interest in photochemical reactions, because of their unique photophysical properties.[17] We hypothesized that an *O*-nitrobenzyl hydroxamate might form an EDA complex with an amine, since nitroarenes are known electrophiles, able to form EDA complexes with electron-rich molecules. To explore the possibility of the formation of an EDA complex between *N*-(2-nitrobenzyloxy)benzamide and either Et_3N or DIPEA and their properties, DFT studies were performed at ωB97X-D[18]/def2-TZVP[19] level of theory, in ACN solvent, using the continuum polarized solvent model (PCM).[20] The lowest in energy geometries of the ground states (S_0) of the EDA complexes are depicted in Figure 1 (for details, see Supporting Information),[21] while the binding energies are summarized in Table 3. In both cases, the calculated ΔE_{bind} values are negative, concluding to the fact that both DIPEA and Et_3N have indeed the ability to form EDA complexes with *N*-(2-nitrobenzyloxy)benzamide, specifically by interacting with the electron-deficient aromatic ring of the substrate, as it is shown by the calculated HOMO and LUMO orbitals, where is evident that charge transfer from the amines to the nitro-substituted aromatic ring takes place (Figure 1). Stronger binding energy is observed for the *N*-(2-nitrobenzyloxy)benzamide-Et_3N pair at −3.9 kcal/mol, while the binding energy of the *N*-(2-nitrobenzyloxy)benzamide-DIPEA complex was found to be at −2.7 kcal/mol (Table 3). Note that

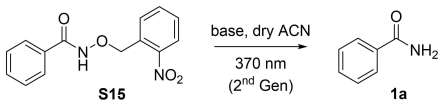
Table 1. Effect of the light source.



Entry	Irradiation wavelength (nm)	Yield (%)[a]
1	370	67
2	**370 (2nd gen)**	**70**
3	390	57
4	427	67
5	440	69
6	456	41
7	467	28
8	525	–
9	CFL	54

Reaction conditions: *N*-(2-nitrobenzyloxy)benzamide (0.10 mmol, 27 mg), DIPEA (0.05 mmol, 9 μL), dry ACN (1 mL), light irradiation at r.t. for 16 h, [a] Yield of product after isolation by column chromatography.

Table 2. Effect of the amine additive.



Entry	Amine	Yield (%)[a]
1	DIPEA	70
2	**Et_3N**	**76**
3	*N*-Methylpyrrolidine	72
4	DABCO	70
5	DBU	66
6	DMAP	58
7	*N*-Methylmorpholine	54
8	Pyridine	27
9	K_2CO_3	48
10[b]	K_2CO_3	43

Reaction conditions: *N*-(2-nitrobenzyloxy)benzamide (0.10 mmol, 27 mg), additive (0.05 mmol), dry ACN (1 mL), light irradiation at 370 nm (2nd Gen) at r.t. for 16 h, [a] Yield of product after isolation by column chromatography, [b] Solvent system ACN/H_2O (1/0.5).

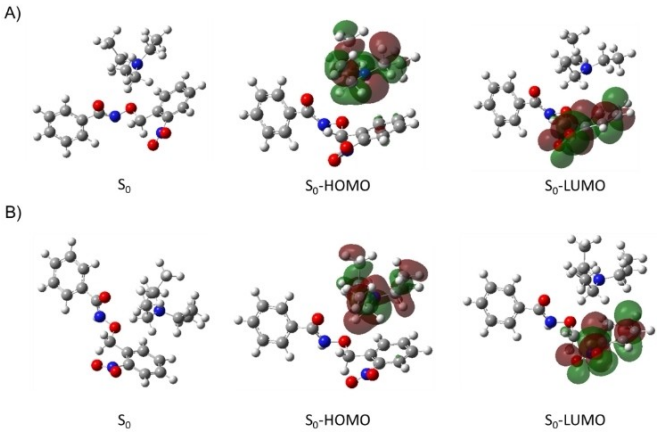


Figure 1. Calculated geometries (S_0 state) and frontier orbitals of: A) Et_3N-*N*-(2-nitrobenzyloxy)benzamide complex and B) DIPEA-*N*-(2-nitrobenzyloxy)benzamide complex at the ωB97X–D/def2-TZVP method.

Table 3. Computed theoretical binding energies ΔE_{bind}, (kcal mol^{-1}) of the EDA complexes in ACN solvent at the ωB97X–D/def2-TZVP level of theory.

EDA Complex	ΔE(BSSE corrected)
N-(2-nitrobenzyloxy)benzamide-Et_3N	−3.9
N-(2-nitrobenzyloxy)benzamide-DIPEA	−2.7

the mentioned values were calculated after corrections related to the Basis Set Superposition Error (BSSE).[22]

Additionally, the N···C (aromatic ring) bond distances were calculated (see Supporting Information).[21] According to the acquired results, the N atoms of the amines are closer to the C3 and C4 carbon atoms of the aromatic ring (Figure 2). Specifically, the N···C distances in the case of *N*-(2-nitrobenzyloxy)benzamide-Et_3N pair are at 3.3 Å and 3.6 Å, respectively, while for the *N*-(2-nitrobenzyloxy)benzamide-DIPEA pair, the corresponding bond distances are at 3.4 Å and 3.7 Å, respectively. These slight differences between the studied complexes may be attributed to stereochemical restrictions, due to the bulky isopropyl groups of DIPEA, thus explaining both the computed N···C distances and the fact that *N*-(2-nitrobenzyloxy)benzamide-Et_3N complex binds stronger. Furthermore, Time Dependent DFT (TD-DFT,[23] TD-ωB97X–D/def2-TZVP methodology) was employed for calculating the energies and geometries of the first excited singlet states (S_1 states) of *N*-(benzyloxy)benzamide, *N*-(2-nitrobenzyloxy)benzamide and the pairs *N*-(2-nitrobenzyl)oxy)benzamide-Et_3N, *N*-(2-nitrobenzyloxy)benzamide-DIPEA, in order to examine how the presence of an *ortho*-nitro group and an amine affect the studied chemical systems and transformations. The corresponding results are depicted in Figure 3. As shown in Figure 3, both the *ortho*-nitro group in the aromatic ring and the base play a pivotal role in reducing the $S_0 \rightarrow S_1$ transition energy. Comparing cases A and B, where the substrates differ only by the presence or absence of a nitro group, it is observed that the $S_0 \rightarrow S_1$ transition energy is approximately 10 kcal/mol lower for the *N*-(2-nitrobenzyloxy)benzamide compound. When Et_3N or DIPEA form EDA complexes with *N*-(2-nitrobenzyloxy)benzamide, the $S_0 \rightarrow S_1$ excitation energy is significantly lower, compared to the case without the base. Specifically, in both cases, the excitation energy is calculated to be 51.2 kcal/mol, which is about 24 kcal/mol lower than that of *N*-(2-nitrobenzyloxy)benzamide alone. These results indicate that the studied EDA complexes are more likely to undergo the next steps of photochemical transformations under UVA irradiation. Moreover, the N···C (aromatic ring) bond distances of the EDA complexes in the S_1 states were calculated and compared to those in the S_0 states (see Supporting Information).[21] Notable changes are observed upon excitation. Specifically, the nitrogen atom of the bases moves away from the C3 and C4 carbon atoms of the substrate, elongating by 0.8–0.9 Å. Conversely, it moves significantly closer to the C1 (*ipso*) carbon atom, where the nitro group is covalently bonded, with a shortening of the N···C bond distance by 1.0–1.3 Å. These results indicate that, upon excitation, a single electron transfer (SET) from the amine to the substrate is likely to occur. The *ipso* position is the most suitable site for this electron transfer, as the resulting radical anion can be better stabilized by the electron-withdrawing nitro group.

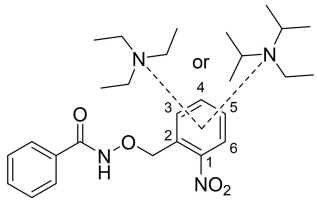


Figure 2. Calculated interactions between the amine and 2-nitrobenzyl substrate.

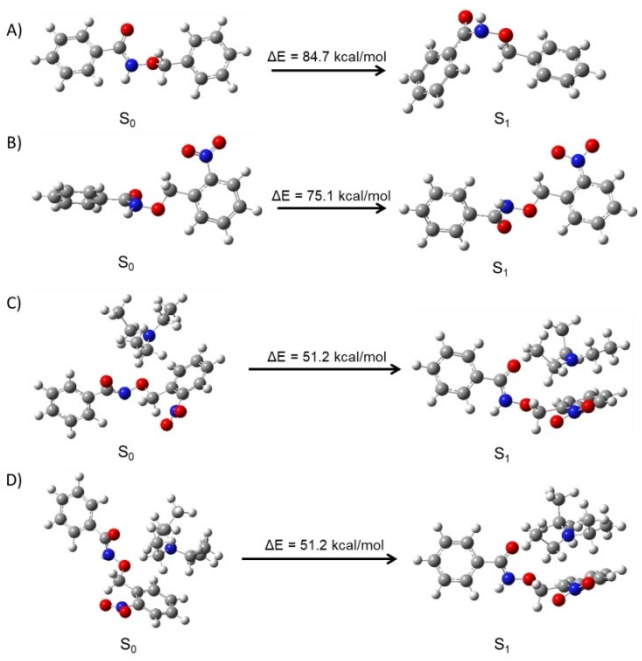


Figure 3. Calculated $S_0 \rightarrow S_1$ transitions energies and S_1 geometries (TD-ωB97X–D/def2-TZVP methodology) of; A) *N*-(benzyloxy)benzamide B) *N*-(2-nitrobenzyloxy)benzamide C) *N*-(2-nitrobenzyloxy)benzamide-Et_3N pair and D) *N*-(2-nitrobenzyloxy)benzamide-DIPEA pair, all in ACN.

The formation of an EDA complex can be experimentally observed via UV-Vis spectroscopy by the appearance of a new band shifted to higher wavelengths, upon mixing the two components.[24] Thus, the UV-Vis spectra of each amine (Et_3N or DIPEA) and *N*-(2-nitrobenzyloxy)benzamide alone and of their mixtures (1 : 1 mole ratio, specifically 0.1 M:0.1 M), were recorded in ACN (5 mL). The UV-Vis spectra are depicted in Figure 4. In both cases, the addition of *N*-(2-nitrobenzyloxy)benzamide into a solution of the base caused a small red shift, indicating the formation of an EDA complex. The red shift is more pronounced in the Et_3N-*N*-(2-nitrobenzyloxy)benzamide pair, compared to the DIPEA-*N*-(2-nitrobenzyloxy)benzamide pair, which aligns with the performed computational results, showing stronger binding energy for the former.

Additional UV-Vis spectra of a series of Et_3N-*N*-(2-nitrobenzyloxy)benzamide solutions were recorded to identify the stoichiometric ratio between donor and acceptor and determine the association constant of the EDA complex in ACN. Using Job's plot method,[25] a 1 : 1 stoichiometry for the absorbing species was identified, and the Benesi-Hildebrand method[26] was employed to determine the association constant, which was found to be 4.44 M^{-1} (see Supporting Information).[21]

Further optimization studies for the synthetic reaction were carried out to explore the role of solvent, amine loading and reaction time. All studied solvents afforded the desired product

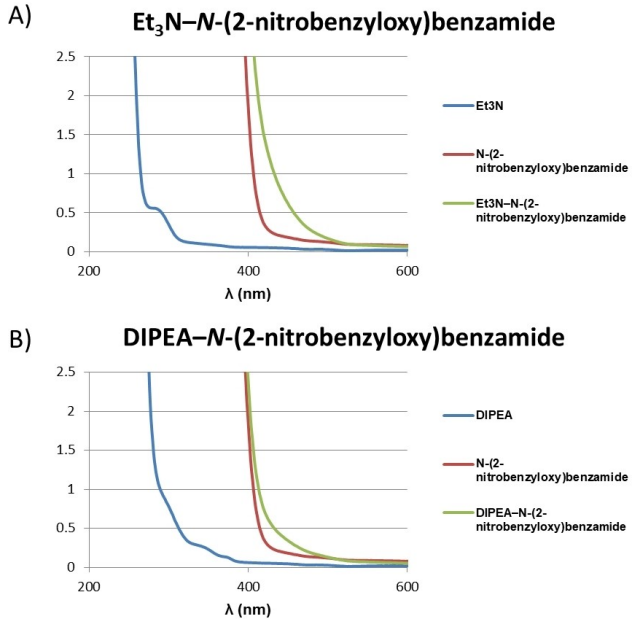
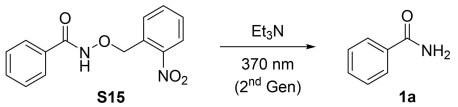


Figure 4. UV-Vis absorbance in acetonitrile (5 mL) of A) Et_3N (0.5 mmol), *N*-(2-nitrobenzyloxy)benzamide (0.5 mmol) and Et_3N-*N*-(2-nitrobenzyloxy)benzamide (0.5 mmol:0.5 mmol), B) DIPEA (0.5 mmol), *N*-(2-nitrobenzyloxy)benzamide (0.5 mmol) and DIPEA-*N*-(2-nitrobenzyloxy)benzamide (0.5 mmol:0.5 mmol).

in good to high yields (Table 4, entries 1–6), where the highest yield was achieved in ACN (Table 4, entry 2). The use of dry ACN resulted in the desired product with comparable yields, suggesting that trace amounts of water do not impact the reaction outcome (Table 4, entry 1). Moreover, chlorinated solvents (Table 4, entries 3 and 4), polar protic (Table 4, entry 5) or aprotic solvents (Table 4, entry 6) afforded the desired product in good to moderate yields. This indicates that the reaction occurs effectively across different solvent types, although the yields may vary. Subsequently, the effect of amine loading was studied (Table 4, entries 7–9). The yield remained high (70–78%) even when 1 or 0.25 equivalents of amine were used (Table 4, entries 7–8), while significant reduction of the amine loading also afforded the desired product, albeit in lower yield (Table 4, entry 9). However, the use of 0.5 equiv. of amine loading was deemed more appropriate for the reaction protocol. This choice was supported by the observation of a substantial 78% yield of the desired product, and its convenience for small-scale experiments. Afterwards, the reaction time was studied (Table 4, entries 10 and 11). Gratifyingly, a yield of 82% was obtained by shortening the reaction time to 2 hours (Table 4, entry 11), with a still respectable yield of 66% achieved by reducing the reaction time to 30 min (Table 4, entry 10), mainly due to incomplete conversion of the starting material. Moreover, the presence of water disrupts the efficiency of the process, leading to inferior results (Table 4, entry 12).

Table 4. Effect of the solvent, amine loading and reaction time.

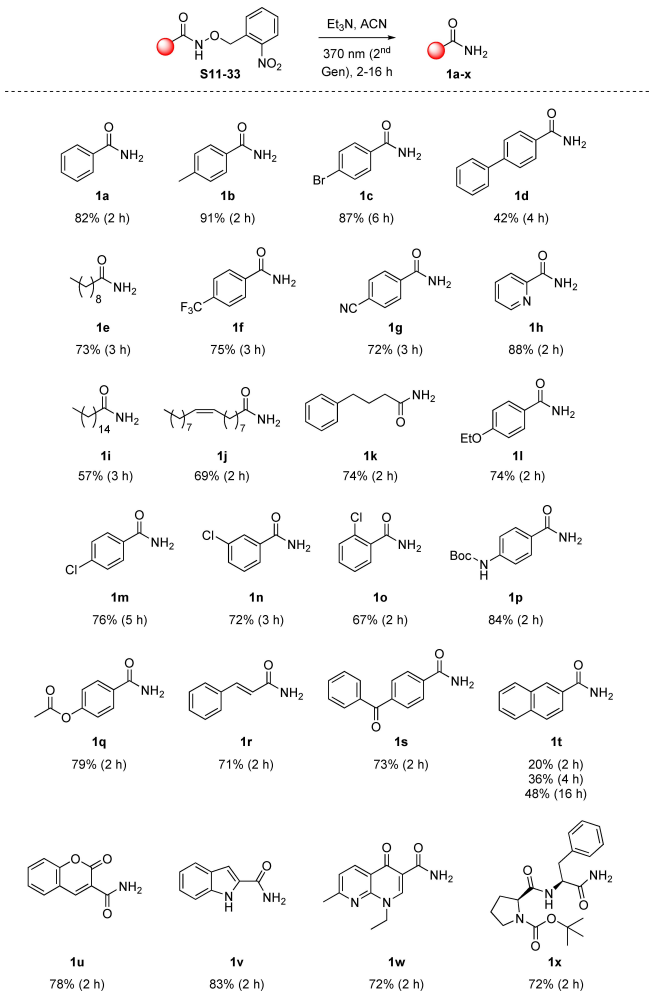


S15 1a

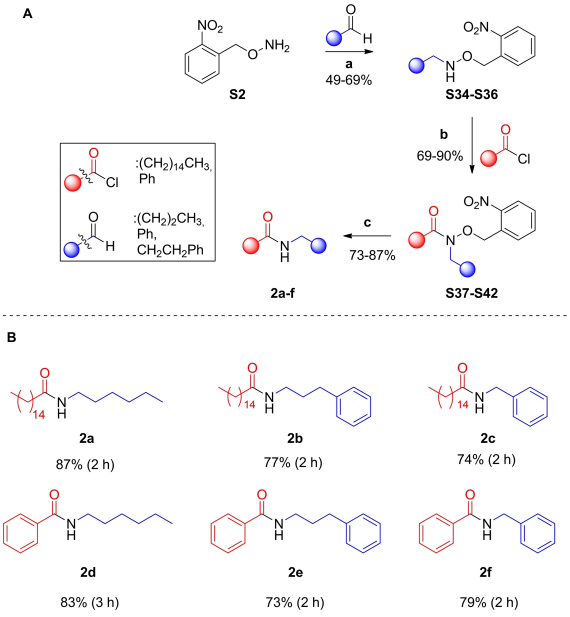
Entry	Solvent	Amine loading (mmol)	Time (h)	Yield (%)[a]
1	dry ACN	0.05	16	76
2	**ACN**	**0.05**	**16**	**78**
3	CH_2Cl_2	0.05	16	60
4	$CHCl_3$	0.05	16	53
5	MeOH	0.05	16	50
6	DMSO	0.05	16	45
7	ACN	0.1	16	70
8	ACN	0.025	16	72
9	ACN	0.01	16	53
10	ACN	0.05	0.5	66
11	**ACN**	**0.05**	**2**	**82**
12[b]	ACN/H_2O	0.05	2	65

Reaction conditions: *N*-(2-nitrobenzyloxy)benzamide (0.10 mmol, 27 mg), Et_3N, solvent (1 mL), light irradiation at 370 nm (2nd Gen) at r.t., [a] Yield of product after isolation by column chromatography, [b] Solvent system ACN/H_2O (1/0.5).

After conducting optimization studies, we identified the optimal reaction conditions, which involved the use of 0.5 equiv. of Et_3N as a base in ACN for a duration of 2 hours. To explore the substrate scope of this new photochemical protocol, various carboxylic acids were coupled with *O*-(2-nitrobenzyl)-hydroxylamine (for full synthetic procedures of starting materials, see Supporting Information),[21] affording the desired *O*-2-nitrobenzyl hydroxamates. The results of the N–O bond cleavage of various *O*-2-nitrobenzyl hydroxamates leading to primary amides are summarized in Scheme 4. We were very pleased to observe that both aliphatic (**1e**, **1i–k**) and aromatic substrates (**1a–d**, **1f–h** and **1l–w**) afforded the desired products in good to high yields, especially since the N–O bond cleavage did not take place in the case of *O*-benzyl hydroxamates of aliphatic acids in previous experiments, in the presence of a catalyst (Scheme 2 vs Scheme 4). Aliphatic saturated substrates afforded the corresponding amides **1e**, **1i** and **1k** in good to high yields (57–74%). Palmitoyl amide (**1i**) was isolated in 57% yield, possibly due to the low solubility of the *N*-(2-nitrobenzyloxy)palmitamide in ACN. Oleyl amide (**1j**) was isolated in 69% yield, indicating that unsaturated substrates are compatible with this protocol. Furthermore, a diverse range of *O*-2-nitrobenzyl hydroxamates of aromatic acids afforded the corresponding benzamides in good to excellent yields (up to 91%). Electron-poor substrates enabled facile access to benzamides **1c**, **1f** or **1g** in high yields (87%, 75% and 72%, respectively). Electron-rich substrates also afforded the desired benzamides **1b** or **1l** in high to excellent yields (91% and 74%, respectively), suggesting that the optimized conditions can be applied to a series of substrates, with both electron-donating and electron-withdrawing functional groups. Consequently, we examined the effect of an *ortho*-, *meta*- and *para*-chloro group in the N–O cleavage of the *O*-2-nitrobenzyl hydroxamates of benzoic acid. *para*-Chloro benzamide **1m** was isolated in a higher yield (76%) than *meta*-chloro benzamide **1n** (72%), which was isolated in a higher yield than *ortho*-chloro



Scheme 4. Substrate scope for the conversion of *O*-2-nitrobenzyl hydroxamates to primary amides. Optimum reaction conditions refer to: hydroxamate (0.10 mmol), Et_3N (0.05 mmol) in ACN (1 mL).

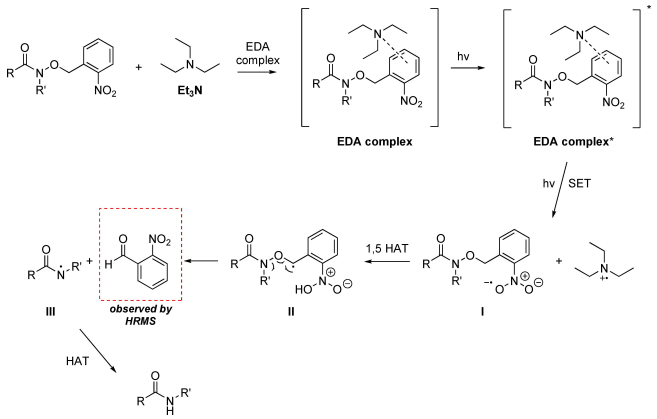


Scheme 5. Substrate scope for the conversion of *O*-2-nitrobenzyl hydroxamates to secondary amides. Reaction conditions: a) AcOH, $NaBH_3CN$, 16 h, b) DMAP, pyridine, dry CH_2Cl_2, under Ar, 16 h, c) hydroxamate (0.10 mmol), Et_3N (0.05 mmol) in ACN (1 mL), 370 nm (2nd Gen), 2–3 h.

benzamide **1o** (67%), indicating that sterically-hindered substrates lead to the corresponding benzamides in lower yields. Additionally, the presence of widely used protecting groups was well-tolerated, providing benzamides **1p** or **1q** in high yields (84% and 79%, respectively). Biphenyl, cinnamoyl or benzoyl based moieties were also compatible with this protocol, affording benzamides **1d**, **1r** or **1s** in good to high yields (up to 73%). In the case of the 2-naphthyl substrate, even though the reaction time was extended to 4 or 16 hours, benzamide **1t** was produced in low yields (36% and 48%, respectively). More challenging examples include heterocyclic benzamides **1h**, **1u** or **1v**, which were accessed in high yields (88%, 78% and 83%, respectively). Furthermore, it was gratifying to produce benzamide **1w**, an analogue of the quinolone antibiotic nalidixic acid, in 72% yield.[27] Finally, application of the protocol to a small peptide-derived *O*-2-nitrobenzyl hydroxamate afforded amide **1x** in high yield (72%).

Then, we turned our focus on the synthesis of secondary amides and the results are summarized in Scheme 5. The desired *O*-2-nitrobenzyl derivatives were accessed via reductive amination of the corresponding aldehyde with *O*-(2-nitrobenzyl)hydroxylamine, followed by coupling with the corresponding acyl chloride (Scheme 5). Both aliphatic and aromatic acyl substrates were used, leading to a variety of tertiary amides (Scheme 5, **A**). Gratifyingly, all tertiary amides afforded the secondary amides in high yields (up to 87%, Scheme 5, B). Palmitoyl amide **2a** was isolated in a higher yield than palmitoyl amides **2b** or **2c** (87% vs 77% and 74%). Benzoyl tertiary amides afforded benzamides **2d**, **2e** or **2f** in high yields (up to 83%).

Based on all the above data, a plausible mechanism may be proposed, as shown in Scheme 6. As indicated by the UV experiments, Et_3N and *O*-2-nitrobenzyl hydroxamate spontaneously form an EDA complex. Upon irradiation at 370 nm (2nd gen), *O*-2-nitrobenzyl hydroxamate-Et_3N EDA complex is excited and upon Single Electron Transfer (SET) from the amine to the



Scheme 6. Proposed mechanism for the photochemical N–O bond cleavage of *O*-2-nitrobenzyl protected hydroxamates.

nitrobenzene moiety, intermediate **I** (Scheme 6) is generated. Subsequently, an 1,5-hydrogen atom transfer (HAT) takes place, leading to the formation of the benzylic radical **II**, followed by the N–O bond cleavage that forms 2-nitrobenzaldehyde and intermediate **III**. Ultimately, another HAT takes place, providing an additional hydrogen atom to intermediate **III**, resulting in the formation of the amide. The formation of 2-nitrobenzaldehyde, as well as product formation, were verified by High Resolution Mass Spectrometry (HRMS) studies.[21]

Conclusions

A novel photochemical method for the N–O bond cleavage of *O*-benzyl type protected hydroxamic acids has been developed. Both *O*-benzyl and *O*-2-nitrobenzyl aromatic hydroxamates were converted to amides under light irradiation (370 nm) in the presence of anthracene, as the catalyst, and a base. However, in the case of *O*-2-nitrobenzyl hydroxamates, the photochemical conversion occurs effectively, requiring only the presence of an amine and avoiding the use of a catalyst. The formation of an EDA complex between the *O*-2-nitrobenzyl hydroxamate and organic bases, such as DIPEA or Et_3N, is supported by DFT and UV-Vis studies. Various aliphatic and aromatic *O*-2-nitrobenzyl hydroxamates afforded a series of primary and secondary amides, showcasing the compatibility of this photochemical protocol to an extensive variety of substrates. A plausible mechanism was proposed, suggesting the initial formation of an EDA complex between Et_3N and *O*-2-nitrobenzyl hydroxamates, assisting the N–O bond cleavage and leading to the amide product. Thus, an efficient metal-free photochemical protocol for N–O bond cleavage of *O*-benzyl type hydroxamates has been demonstrated, providing new evidence for the reactivity of the N–O bond in the hydroxamic acid functionality under diverse conditions.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[28–61]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[1] For selected reviews, see: a) M. Thomas, J. Alsarraf, N. Araji, I. Tranoy-Opalinski, B. Renoux, S. Papot, *Org. Biomol. Chem.* **2019**, *17*, 5420–5427; b) A. Citarella, D. Moi, L. Pinzi, D. Bonanni, G. Rastelli, *ACS Omega* **2021**, *6*, 21843–21849.
[2] For selected reviews, see: a) T. C. S. Ho, A. H. Y. Chan, A. Ganesan, *J. Med. Chem.* **2020**, *63*, 12460–12484; b) M. Su, X. Gong, F. Liu, *Expert Opin. Drug Discov.* **2021**, *16*, 745–761.
[3] For a review, see: J. Keth, T. Johann, H. Frey, *Biomacromolecules* **2020**, *21*, 2546–2556.
[4] L. E. Fisher, J. M. Caroon, Jahangir, S. R. Stabler, S. Lundberg, J. M. Muchowski, *J. Org. Chem.* **1993**, *58*, 3643–3647.
[5] M. Yus, G. Radivoy, F. Alonso, *Synthesis* **2001**, *6*, 914–918.
[6] S. Wang, X. Zhao, D. Zhang-Negreriea, Y. Du, *Org. Chem. Front.* **2019**, *6*, 347–351.
[7] T. You, M. Zhang, J. Chen, H. Liu, Y. Xia, *Org. Chem. Front.* **2021**, *8*, 112–119.
[8] M. Malik, R. Senatore, T. Langer, W. Holzera, V. Pace, *Chem. Sci.* **2023**, *14*, 10140–10146.
[9] For selected recent reviews, see: a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; b) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41–49; c) M. A. Theodoropoulou, N. F. Nikitas, C. G. Kokotos, *Beilstein J. Org. Chem.* **2020**, *16*, 833–857; d) N. F. Nikitas, P. L. Gkizis, C. G. Kokotos, *Org. Biomol. Chem.* **2021**, *19*, 5237–5253; e) A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath, D. W. C. MacMillan, *Chem. Rev.* **2022**, *122*, 1485–1542; f) L. Capaldo, D. Ravelli, M. Fagnoni, *Chem. Rev.* **2022**, *122*, 1875–1924; g) P. L. Gkizis, *Eur. J. Org. Chem.* **2022**, *2022*, e202201139 ; h) E. Skolia, O. G. Mountanea, C. G. Kokotos, *Trends Chem.* **2023**, *5*, 116–120; i) J.-H. Shen, M. Shi, Y. Wei, *Chem. Eur. J.* **2023**, *29*, e202301157.
[10] For selected reviews, see: a) F. Xiao, Y. Guo, Y.-F. Zeng, *Adv. Synth. Catal.* **2021**, *363*, 120–143; b) H.-M. Jiang, Y.-L. Zhao, Q. Sun, X.-H. Ouyang, J.-H. Li, *Molecules* **2023**, *28*, 1775.
[11] For selected references, see: a) T. Patra, P. Bellotti, F. Strieth-Kalthoff, F. Glorius, *Angew. Chem. Int. Ed.* **2020**, *59*, 3172–3177; b) T. Patra, S. Mukherjee, J. Ma, F. Strieth-Kalthoff, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 10514–10520.
[12] K. S. Troelsen, E. D. D. Calder, A. Skwarska, D. Sneddon, E. M. Hammond, S. J. Conway, *ChemMedChem* **2021**, *16*, 3691–3700.
[13] J. Soika, C. McLaughlin, T. Neveselý, C. G. Daniliuc, J. J. Molloy, R. Gilmour, *ACS Catal.* **2022**, *12*, 10047–10056.
[14] H. Li, C. Wang, F. Glaser, N. Sinha, O. S. Wenger, *J. Am. Chem. Soc.* **2023**, *145*, 11402–11414.
[15] For contributions from our group employing organic molecules in photochemical reactions, see: a) C. S. Batsika, C. Mantzourani, D. Gkikas, M. G. Kokotou, O. G. Mountanea, C. G. Kokotos, P. K. Politis, G. Kokotos, *J. Med. Chem.* **2021**, *64*, 5654–5666; b) E. Skolia, P. L. Gkizis, N. F. Nikitas, C. G. Kokotos, *Green Chem.* **2022**, *24*, 4108–4118; c) E. Skolia, P. L. Gkizis, C. G. Kokotos, *Org. Biomol. Chem.* **2022**, *20*, 583–5844; d) P. L. Gkizis, S. K. Serviou, A. Balaskas, C. T. Constantinou, I. Triandafillidi, C. G. Kokotos, *Synlett* **2023**, *35*, 330–336; e) O. G. Mountanea, C. Mantzourani, M. G. Kokotou, C. G. Kokotos, G. Kokotos, *Eur. J. Org. Chem.* **2023**, *26*, e202300046; f) A. Bourboula, O. G. Mountanea, G. Krasakis, C. Mantzourani, M. G. Kokotou, C. G. Kokotos, G. Kokotos, *Eur. J. Org. Chem.* **2023**, *26*, e202300008; g) E. Skolia, O. G. Mountanea, C. G. Kokotos, *Chem-*

SusChem **2024**, *17* e202400174; h) O. G. Mountanea, E. Skolia, C. G. Kokotos, *Chem. Eur. J.* **2024**, *30*, e202401588.
[16] For comprehensive reviews and historical evolution of the field, see: a) C. G. Bochet, *J. Chem. Soc. Perkin Trans. 1* **2002**, 125–142; b) P. Klan, T. Solomek, C. G. Bochet, A. Blank, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev.* **2013**, *113*, 119–191.
[17] P. L. Gkizis, I. Triandafillidi, C. G. Kokotos, *Chem* **2023**, *9*, 3401–3414.
[18] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
[19] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.
[20] M. Cozi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43–54.
[21] For detailed methods and results, see Supporting Information.
[22] M. Gutowski, G. Chalasinki, *J. Chem. Phys.* **1993**, *98*, 5540–5554.
[23] M. E. Casida in Recent Advances in Density Functional Theory, (D. P. Chang), World Scientific, Singapore **1995**, 155–192.
[24] For selected references: a) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* **2013**, *42*, 1667–1680; b) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478–2601; c) O. G. Mountanea, D. Psathopoulou, C. Mantzourani, M. G. Kokotou, E. A. Routsi, D. Tzeli, C. G. Kokotos, G. Kokotos, *Chem. Eur. J.* **2023**, *29*, e2023005; d) E. A. Routsi, C. Mantzourani, M. Rrapi, O. G. Mountanea, M. G. Kokotou, D. Tzeli, C. G. Kokotos, G. Kokotos, *ChemPlusChem* **2024**, *89*, e202400019.
[25] J. S. Renny, L. L. Tomasevich, E. H. Tallmadge, D. B. Collum, *Angew. Chem. Int. Ed.* **2013**, *52*, 11998–12013.
[26] H. A. Benesi, J. H. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
[27] R. Gleckman, S. Alvarez, D. W. Joubert, S. J. Matthews, *Am. J. Hosp. Pharm.* **1979**, *36*, 1071–1076.
[28] J. Su, J.-N. Mo, X. Chen, A. Umanzor, Z. Zhang, K. N. Houk, J. Zhao, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112668.
[29] I. A. P. Samuel Rajan, S. Rajendran, *Org. Biomol. Chem.* **2023**, *21*, 4760–4765.
[30] R. Hernández-Ruiz, S. Gómez-Gil, M. R. Pedrosa, S. Suárez-Pantiga, R. Sanz, *Org. Biomol. Chem.* **2023**, *21*, 7791–7798.
[31] K. Govindan, W.-Y. Lin, *Org. Lett.* **2021**, *23*, 1600–1605.
[32] T. Ezawa, Y. Kawashima, T. Noguchi, S. Jung, N. Imai, *Tetrahedron: Asymmetry* **2017**, *28*, 1690–1699.
[33] S. Ghosh, C. K. Jana, *J. Org. Chem.* **2018**, *83*, 260–266.
[34] F. Dalu, M. A. Scorciapino, C. Cara, A. Luridiana, A. Musinu, M. Casu, F. Secci, C. Cannas, *Green Chem.* **2018**, *20*, 375–381.
[35] X.-J. Dai, H. Wang, C.-J. Li, *Angew. Chem. Int. Ed.* **2017**, *129*, 6399–6403.
[36] T. Yamamoto, H. Togo, *Eur. J. Org. Chem.* **2018**, *2018*, 4187–4196.
[37] S. Gupta, A. Ansari, K. V. Sashidhara, *Tetrahedron Lett.* **2019**, *60*, 151076.
[38] X. Ma, D. Liu, X. Wan, J. Zhao, *Synth. Commun.* **2023**, *53*, 503–510.
[39] J. Chen, Y. Xia, S. Lee, *Org. Lett.* **2020**, *22*, 3504–3508.
[40] a) R. Cremlyn, F. Swinbourne, J. Atherall, L. Courtney, T. Cronje, P. Davis, S. Langston, M. Rogers, *Phosphorus Sulfur Relat. Elem.* **1980**, *9*, 155–164; b) B. D. Anderson, R. A. Conradi, *J. Pharm. Sci.* **1980**, *69*, 424–430.
[41] H. Wu, A. Sumita, Y. Otani, T. Ohwada, *J. Org. Chem.* **2022**, *87*, 15224–15249.
[42] a) S. M. Kovalenko, I. E. Bylov, K. M. Sytnik, V. P. Chernykh, Y. V. Bilokin, *Molecules* **2000**, *5*, 1146–1165; b) T. E. Ali, M. A. Assiri, H. M. El-Shaaer, M. M. Hassan, A. M. Fouda, N, M. Hassanin, *Synth. Commun.* **2019**, *49*, 2983–2994.
[43] V. A. Mamedov, V. L. Mamedova, V. V. Syakaev, G. Z. Khikmatova, D. E. Korshin, T. A. Kushatov, S. K. Latypov, *Tetrahedron Lett.* **2018**, *59*, 3923–3925.
[44] G. Y. Lesher, M. D. Gruett, BE612258A, **1962**.
[45] H. Sone, T. Nemoto, M. Ojika, K. Yamada, *Tetrahedron Lett.* **1993**, *34*, 8445–8448.
[46] S. Behrouz, M. N. S. Rad, E. Forouhari, *J. Chem. Res.* **2016**, *40*, 101–106.
[47] R. Zhang, W.-Z. Yao, L. Qian, W. Sang, Y. Yuan, M.-C. Du, H. Cheng, C. Chen, X. Qin, *Green Chem.* **2021**, *23*, 3972–3982.
[48] H. Keum, H. Ryoo, D. Kim, S. Chang, *J. Am. Chem. Soc.* **2024**, *146*, 1001–1008.
[49] V. Kumar, S. J. Connon, *Chem. Commun.* **2017**, *53*, 10212–10215.
[50] a) D. P. Sebesta, S. S. O' Rourke, R. L. Martinez, W. A. Pieken, D. P. C. McGee, *Tetrahedron* **1996**, *52*, 14385–14402; b) Y. Zhou, V. Bharadwaj, M. S. Rahman, P. Sampson, N. E. Brasch, A. J. Seed, *J. Photochem. Photobiol. A Chem.* **2019**, *384*, 112033.
[51] S. M. Canham, D. J. France, L. E. Overman, *J. Org. Chem.* **2013**, *78*, 9–34.
[52] S. S. More, R. Vince, *J. Med. Chem.* **2009**, *52*, 4650–4656.
[53] K. J. Berger, B. D. Dherange, M. Morales, J. L. Driscoll, A. K. Tarhan, M. D. Levin, *Org. Synth.* **2023**, *100*, 113–135.
[54] N. F. Nikitas, M. K. Apostolopoulou, E. Skolia, A. Tsoukaki, C. G. Kokotos, *Chem. Eur. J.* **2021**, *27*, 7915–7922.
[55] Y. Jia, B. Schroeder, Y. Pfeifer, C. Fröhlich, L. Deng, C. Arkona, B. Kuropka, J. Sticht, K. Ataka, S. Bergemann, G. Wolber, C. Nitsche, M. Mielke, H.-K. S. Leiros, G. Werner, J. Rademann, *J. Med. Chem.* **2023**, *66*, 11761–11791.
[56] W. R. Grither, J. Korang, J. P. Sauer, M. P. Sherman, P. L. Vanegas, M. Zhang, R. D. McCulla, *J. Photochem. Photobiol. A Chem.* **2012**, *227*, 1–10.
[57] F. B. Van Duijneveldt, J. G. C. M. Van Duijneveldt-Van De Rijdt, J. H. Van Lenthe, *Chem. Rev.* **1994**, *94*, 1873–1885.
[58] A. Chantzis, A. D. Laurent, C. Adamo, D. Jacquemin, *J. Chem. Theory Comput.* **2013**, *9*, 4517–4525.
[59] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[60] Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.
[61] S. C. Blackstock, J. P. Lorand, J. K. Kochi, *J. Org. Chem.* **1987**, *52*, 1451–1460.

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