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RESEARCH ARTICLE

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An Efficient Light-mediated Protocol for the Direct Amide Bond Formation via a Novel Carboxylic Acid Photoactivation Mode by Pyridine–CBr_4

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To the memory of Leonidas Zervas, who together with Max Bergmann introduced the carbobenzoxy group 90 years ago

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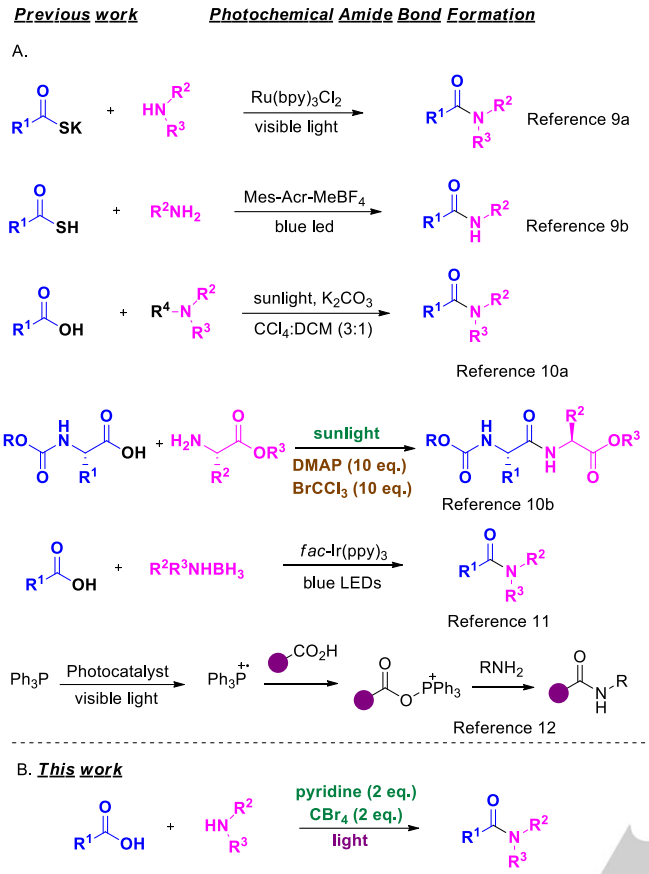
Abstract: The direct amide bond formation between a carboxylic acid and an amine still constitutes a challenging reaction for both academia and industry. We demonstrate herein that several pairs of amines (halogen bond acceptors) and organohalogen sources may be used for the photochemical amidation reaction under either UVA or sunlight irradiation. Our studies led to the identification of pyridine–CBr_4 as an efficient agent to perform amide synthesis under LED 370 nm irradiation, avoiding super-stoichiometric quantities. An extended substrate scope was demonstrated, showing that the widely used amino and carboxyl protecting groups are compatible with this photochemical protocol, while a number of industrially interesting products and bioactive compounds were synthesized. Direct infusion–high resolution mass spectrometry studies suggest an unprecedented type of carboxylic acid activation mode upon irradiation, involving the generation of a symmetric anhydride, an active ester with pyridine *N*-oxide and a mixed anhydride with hypobromous acid.

Introduction

In the 21st century, the synthesis of the amide bond and the amino acid coupling still remains a challenging reaction. As highlighted in various review articles,[1] the formation of the amide bond is one of the most frequently performed reactions, either in academia or in industry, possessing a 16% share of the total reactions used for the synthesis of new drugs.[1c] In a 2006 survey, it was estimated that an amide bond was present in 2/3 of drugs candidates,[1a] while our own search among the top 200 best-selling drugs in 2021[2] revealed that at least 66 contained one amide bond.

So far, the method which possesses the lion's share in the amide bond formation and the peptide coupling involves the employment of coupling reagents.[3] This widely used methodology requires the use of expensive reagents, often used in excess, in particular in solid phase peptide synthesis. In addition, some coupling reagents require demanding methods for their synthesis. As a consequence, during the last fifteen years considerable efforts have been devoted to the development of alternative methods, exploring non-classical routes.[4] The development of catalytic methods are of high interest, however they have not flourished up to now, although interesting advances have been achieved.[5] In any case, novel methods for amide bond formation are anticipated to have a high impact in industry, since large-scale amidations are very important in process chemistry.[6]

In recent years, synthetic photochemistry and photocatalysis have captured the attention and imagination of organic chemists, offering solutions to long-standing synthetic problems and the possibility to discover novel reactivities.[7] The field of amide bond formation has not been unaffected by this revolutionary wave and several protocols for the visible light-mediated amide synthesis have been reported using various starting materials.[8] In 2016, a remarkable visible-light-promoted photoredox catalytic methodology was demonstrated starting from ecofriendly potassium thioacids and amines, employing $Ru(bpy)_3Cl_2$ as the photocatalyst,[9a] while some years later, a metal-free approach employing 9-mesityl-10-methylacridinium tetrafluoroborate (Mes-Acr-$MeBF_4$) for the coupling of thioacids and amines appeared (Scheme 1, A).[9b] In 2017, Szpilman *et al.* reported the activation of amines under sunlight through a charge-transfer complex (CTC) and the subsequent coupling with acids, however the method was limited mainly in tertiary amines and aromatic acids (Scheme 1, A).[10a] In 2021, Szpilman and coworkers presented a sunlight-mediated coupling of amino acids, which relies on the light activation of a 4-dimethylaminopyridine–bromotrichloromethane (DMAP–$BrCCl_3$) CTC to generate a novel coupling reagent *in situ* (Scheme 1, A).[10b] At the same time, a photocatalytic deoxygenative amidation protocol employing amine-boranes and carboxylic acids was developed and used for the synthesis of a variety of functionalized amides and the late-stage functionalization of several pharmaceuticals (Scheme 1, A).[11] Most recently, Zhao and co-workers have reported the synthesis of amides and peptides through the generation of oxyphosphonium ions by photoredox/cobaloxime catalysis both in batch and continuous-



Scheme 1. Literature methods for the amide bond formation and this work.

flow (Scheme 1, A).[12]

Working in the field of synthetic photochemistry[13] and having developed protocols for the synthesis of amides starting from aldehydes,[14] our attention has been captured by the method presented by Szpilman and coworkers,[10b] which is based on the formation and photoactivation of a DMAP–$BrCCl_3$ complex. However, this method suffers from a serious drawback: the use of super-stoichiometric quantities of DMAP and $BrCCl_3$ (10 equivalents). The aim of our work was to study in detail the ability of selected amines to form halogen bonds (HBs) with various halogen bond donors, in an effort to define the factors that affect the generation of such complexes and their ability to be photoactivated, leading to coupling of carboxylic acids with amine components. UV-Vis and NMR studies, as well as computational calculations, were performed to understand the formation of halogen-bonded complexes (HBCs) and the subsequent successful carboxylic acid-amine coupling. We demonstrate herein that a combination of pyridine and carbon tetrabromide leads to successful coupling reactions of carboxylic acids with amine components, including amino acids, under UVA light irradiation, overcoming the drawback of super-stoichiometric quantities (Scheme 1, B). High resolution mass spectrometry (HRMS)-guided mechanistic studies of this new protocol unraveled an unprecedented activation mode of the carboxylic acid, involving the generation of a symmetric anhydride, an active ester of the carboxylic acid with pyridine *N*-oxide and a mixed anhydride between the carboxylic acid and hypobromous acid, as the active intermediates. The method has a wide substrate scope and can be applied in the synthesis of industrially relevant and bioactive compounds.

Results and Discussion

Although the formation of HBCs and their characterization as CTCs have been reported since the 1950s,[15] only during the last 15 years such complexes have been recognized as efficient species to initiate and perform organic reactions, including organocatalytic or photocatalytic reactions.[16] The photochemical amino acid coupling protocol published by Szpilman, Eichen *et al.* in 2021,[10b] is based on the generation of a DMAP–$BrCCl_3$ complex, which upon sunlight activation leads to a successful coupling reaction. We envisaged that various couples of amines and halomethanes or halogen-containing compounds may form HBCs and subsequently such complexes may be activated by UVA or sunlight to mediate amidation reactions. Initially, we studied the potential formation of HBCs between the amines DMAP, *N,N*-dimethylaniline (DMA) or pyridine (as HB acceptors) and the halomethanes $BrCCl_3$, CBr_4, CCl_4, CH_2Br_2, or the bromine sources *N*-bromosuccinimide (NBS) and $BrCH_2CN$ (as HB donors), in various solvents. DMAP, used by Szpilman *et al.*,[10b] contains two distinct nitrogen atoms able to be involved in halogen bonding. DMA and pyridine were selected in order to understand how each one of the distinct nitrogen atoms (nitrogen of a tertiary amine in DMA or the pyridine nitrogen) behaves in halogen bonding. For each pair of amine and halogen source, we recorded the UV-Vis spectra of the HB acceptor and the HB donor, each one alone, and of mixtures of HB acceptor and HB donor in 5.5:1 and 5.5:5 mole ratios in various solvents (Figures S2-S13).[17] The UV-Vis spectra for the twelve pairs in acetonitrile (ACN), 1,2-dichloroethane (DCE), ethyl acetate (EtOAc) or acetone are shown in the Supporting information (Figures S2-S13).[17] Figure 1 summarizes the UV-Vis spectra for six pairs recorded in ACN.

In all studied solvents, the addition of $BrCCl_3$ into a solution of DMAP caused a red shift, which was clearly enhanced going from 5.5:1 to 5.5:5 mole ratio (Figure S2). This is in accordance with the observation of Szpilman *et al.* for UV-Vis spectra recorded in DCE.[10b] The greatest shift was observed in ACN (Figure 1, A), thus ACN seems to be the most appropriate solvent for the HBC formation. A similar red shift was also observed in the case of DMAP–CBr_4 (Figure 1, B), while for the DMAP–CCl_4 or DMAP–CH_2Br_2 pairs, such a red shift was minimal (Figure S4 and S5).[17] In the case of DMA, the addition of either $BrCCl_3$ or CBr_4 in ACN caused an enormous red shift, which was clearly enhanced going from 5.5:1 to 5.5:5 mole ratio (Figure 1, C and D), while the addition of CCl_4 caused a considerably lower shift and no shift was observed upon addition of CH_2Br_2 (Figure S8 and S9).[17] For pyridine in ACN, a small shift was observed upon addition of either $BrCCl_3$ (Figure 1, E) or CCl_4 (Figure S12)[17] in 5.5:5 mole ratio, while for CBr_4 such a shift was vague (Figure 1, F) and no shift was observed upon addition of CH_2Br_2 (Figure S13).[17]

Halogen bonding propensity in solution is usually predicted by computational approaches and only very recently Raman spectroscopy has found application for direct observation.[18] In the present study, to further understand the interactions between the various HB donors and acceptors, we recorded ^{13}C NMR

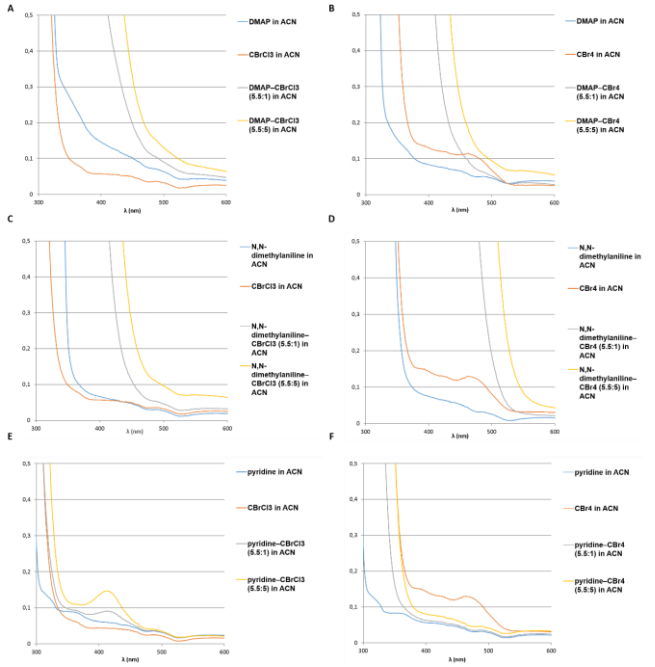


Figure 1. UV-Vis absorbance in acetonitrile (5 mL) of A. DMAP (5.5 mmol), $BrCCl_3$ (5 mmol), DMAP–$BrCCl_3$ (5.5 mmol:1 mmol) and DMAP–$BrCCl_3$ (5.5 mmol:5 mmol), B. DMAP (5.5 mmol), CBr_4 (5 mmol), DMAP–CBr_4 (5.5 mmol:1 mmol) and DMAP–CBr_4 (5.5 mmol:5 mmol), C. DMA (5.5 mmol), $CBrCl_3$ (5 mmol), DMA–$BrCCl_3$ (5.5 mmol:1 mmol) and DMA–$BrCCl_3$ (5.5 mmol:5 mmol), D. DMA (5.5 mmol), CBr_4 (5 mmol), DMA–CBr_4 (5.5 mmol:1 mmol) and DMA–CBr_4 (5.5 mmol:5 mmol), E. pyridine (5.5 mmol), $BrCCl_3$ (5 mmol), pyridine–$BrCCl_3$ (5.5 mmol:1 mmol) and pyridine–$BrCCl_3$ (5.5 mmol:5 mmol), F. pyridine (5.5 mmol), CBr_4 (5 mmol), pyridine–CBr_4 (5.5 mmol:1 mmol) and pyridine–CBr_4 (5.5 mmol:5 mmol).

spectra of a solution of each halomethane alone and the corresponding mixture of halomethane–amine and the shifts observed for halomethane carbon atom are summarized in Table 1. When DMAP was mixed with $BrCCl_3$ or CBr_4 or CCl_4 or CH_2Br_2, the highest shift was recorded for CBr_4 (0.95 ppm, entry 2, Table 1). The shifts observed for CCl_4 (0.29 ppm) or $BrCCl_3$ (0.24 ppm) were similar (entries 1 and 3, Table 1), while the shift for CH_2Br_2 was negligible (0.07 ppm, entry 4, Table 1). For mixtures consisting of DMA and halomethane, a shift was observed only in the case of CBr_4 (0.37 ppm, entry 6, Table 1). For pyridine, again the highest shift was recorded in the case of CBr_4 (0.43 ppm, entry 10, Table 1). Small shifts for CCl_4 or $BrCCl_3$ were also observed, while the shift for CH_2Br_2 was negligible. These results suggest that ^{13}C NMR spectroscopy enables the identification of interactions, suggesting the formation of halogen bonding. For all studied HB acceptors (DMAP, DMA, pyridine), the most notable shifts were observed in the case of CBr_4 as the HB donor.

To further explore the generation of HBCs and their properties, DFT studies (wB97X-D[19]/def2TZVP[20]) in ACN solvent were carried out. The ground state (S_0, singlet) and the lowest calculated in energy triplet state (T_1) of the HBCs DMAP–CBr_4, DMAP–$BrCCl_3$, DMA–CBr_4, DMA–$BrCCl_3$, pyridine–CBr_4 and pyridine–$BrCCl_3$ are depicted in Figure 2 and selected geometries are summarized in Table 2. In the ground states, a weak Br···N bond is formed and the C-Br···N angle is almost linear (see, Table 2). For both DMAP and pyridine, the Br···N bond is about 2.8 Å, while for DMA is about 2.9 Å, due to stereochemical restrictions resulting from the methyl groups.

Table 1. ^{13}C NMR (100 MHz, $CDCl_3$) shifts of halomethane carbon upon mixing with HB acceptors.[17]

Entry	Amine-Halomethane	δ_C ppm before mix	δ_C ppm after mix	Δ ppm
1	DMAP + $BrCCl_3$	67.58	67.34	0.24
2	DMAP + CBr_4	-29.61	-28.66	0.95
3	DMAP + CCl_4	96.15	95.86	0.29
4	DMAP + CH_2Br_2	18.95	18.88	0.07
5	DMA + $BrCCl_3$	67.58	67.55	0.03
6	DMA + CBr_4	-29.61	-29.24	0.37
7	DMA + CCl_4	96.15	96.10	0.05
8	DMA + CH_2Br_2	18.97	18.93	0.04
9	Pyridine + $BrCCl_3$	67.58	67.41	0.17
10	Pyridine + CBr_4	-29.60	-29.17	0.43
11	Pyridine + CCl_4	96.15	95.97	0.18
12	Pyridine + CH_2Br_2	18.95	18.89	0.06

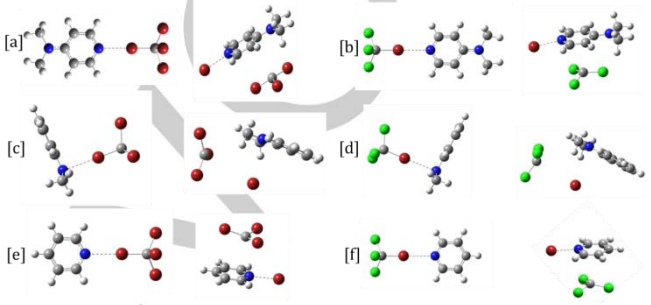


Figure 2. Calculated structures of the halogen-bonded complexes (left) and their first excited triplet states (right) at the wB97X-D/def2TZVP method; a. DMAP–CBr_4, b. DMAP–$BrCCl_3$, c. DMA–CBr_4, d. DMA–$BrCCl_3$, e. Pyridine–CBr_4, f. Pyridine–$BrCCl_3$.

Additionally, its N atom when interacts with Br, has not a planar geometry, and the CCNC dihedral angle is 145.8 degrees. On the contrary, the Br···N bond does not affect the geometries of the N atoms in DMAP and in pyridine. In the lowest in energy triplet states (T_1), the C–Br bond has been cleaved and the $^{\bullet}CBr_3$ and $^{\bullet}CCl_3$ radicals are formed. In the case of DMAP or pyridine, the Br atom is connected to the nitrogen of the pyridine ring, and the Br···N bond becomes shorter by 0.3 Å and 0.35 Å, respectively. On the contrary, in the case of the DMA, the N···Br is elongated by 0.6 Å and the CCNC dihedral angle from 145.6 degrees in the S_0 state becomes almost planar at 171.1 degrees in the T_1 state. Note that changes in the dihedral geometry of the N atom are associated with the properties of compounds.[21]

The strongest binding energy (ΔE_{bind}) is observed for the DMA–CBr_4 pair at -4.59 kcal/mol, even though the N atom of DMA is not planar, while the weakest one is found for the pyridine–$BrCCl_3$ at -3.78 kcal/mol (Table 3). DMA forms the most stable donor-acceptor pairs, and it presents the lowest adiabatic

Table 2. Calculated C–Br and Br···N bond distances (Å), C-Br···N angles (degrees), and CCNC dihedral angles (degrees) for all XB donors and halogen bonded complexes in ACN solvent at the wB97X-D/def2TZVP level of theory.

XB Donor & XB complex	C–Br [a]	C-Br···N [a]	C-Br···N angle[a]	CCNC angle [a]	C-Br···N [b]	CCNC angle [b]
CBr_4	1.938					
DMAP–CBr_4	1.945	2.773	179.99		2.470	
DMA–CBr_4	1.941	2.927	178.69	145.8	3.550	171.1
pyridine–CBr_4	1.943	2.824	179.91		2.482	
$BrCCl_3$	1.944					
DMAP–$BrCCl_3$	1.949	2.781	179.94		2.470	
DMA–$BrCCl_3$	1.946	2.940	179.19	145.7	3.561	171.5
pyridine–$BrCCl_3$	1.947	2.830	179.88		2.483	

[a] Ground state (S_0). [b] First excited triplet state (T_1).

Table 3. Calculated theoretical binding energies (ΔE_{bind} in kcal mol^{-1}) of all halogen-bonded complexes in ACN solvent at the wB97X-D/def2TZVP methodology.

	XB Donors	
XB Acceptors	CBr_4	$BrCCl_3$
DMAP	-4.43	-4.30
DMA	-4.59	-4.37
Pyridine	-3.89	-3.78

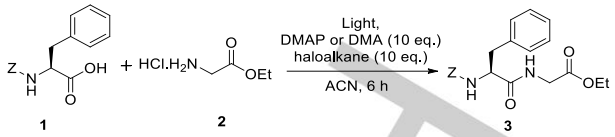
Table 4. Calculated vertical (ΔE_v) and adiabatic (ΔE_a) singlet-triplet excitation energy in kcal mol^{-1} of all halogen-bonded complexes in ACN solvent at the wB97X-D/def2TZVP level of theory.

Halogen-bonded complex	**ΔE_v**	**ΔE_a**
DMAP–CBr_4	87.3	31.2
DMAP–$BrCCl_3$	87.3	33.1
DMA–CBr_4	84.2	24.9
DMA– $BrCCl_3$	84.3	26.1
pyridine–CBr_4	92.3	34.2
pyridine– $BrCCl_3$	92.3	35.7

$S_0 \rightarrow T_1$ excitation energy, i.e., 24.9 kcal/mol (DMA–CBr_4) (Table 4). This means that the triplet state for DMA is thermodynamically the most stable, meaning that it is the least reactive. On the contrary, pyridine forms the less stable donor-acceptor pairs, and it presents the highest adiabatic $S_0 \rightarrow T_1$ excitation energy, 38% than DMA–CBr_4 (Table 4). Thus, we can conclude that pyridine complexes more easily react towards the next steps of the photochemical reaction than the other complexes. All the above spectroscopic and computational studies show that indeed DMAP, DMA and pyridine may form halogen bonds with CBr_4 and $BrCCl_3$, although the properties and the strength of such a bond seem to vary.

Then, we studied the photochemical coupling of Z-L-phenylalanine (Z-Phe-OH, **1**) to ethyl glycinate (H-Gly-OEt, **2**), using DMAP or DMA and various HB donors, under light irradiation. Ten equivalents of DMAP and HB donors ($BrCCl_3$, CBr_4, CCl_4, CH_2Br_2, NBS or $BrCH_2CN$) and two equivalents of the amine component were used in all cases. The results are summarized in Table 5 (full studies are presented in Tables S1 and S2).[17] After a reaction time of 6 h, the highest yield was achieved under LED irradiation at 370 nm in ACN (75% yield, entry 3 vs 1, Table 5), while under sunlight, 67% yield was recorded (entry 4, Table 5). It should be noticed that using 2 equivalents of DMAP and $BrCCl_3$, the product was obtained in only 16% yield (entry 2, Table 5). Both CBr_4 and CCl_4 proved less efficient agents, leading to 71% and 65% yield (entries 5 and 7, Table 5) of isolated product under LED 370 nm, while under sunlight, the yield using CBr_4 was 59% (entry 6, Table 5). The result for CBr_4 is in contrast to that reported by Szpilman *et al.*,[10b] reporting no formation of the desired amide product using DMAP–CBr_4 under sunlight. In the case of CCl_4, it is in accordance with Szpilman *et al.*,[10b] who reported that under sunlight, CCl_4 had to be used as a co-solvent to reach a satisfactory yield, requiring extended reaction time and increased excess of the amino component. The other bromine sources used (CH_2Br_2, NBS and $BrCH_2CN$) led to very low yields (entries 8-10, Table 5). The results for the studies using DMA and various HB donors are also presented in Table 5. Similar trends to DMAP were observed after 6 h (entries 11-13, Table 5), and the highest yield of isolated product was 77% (entry 12, Table 5). Lower yields were observed for DMA–CBr_4 (entries 14-16, Table 5), while again a dramatic drop of the yield was observed, when the equivalents of DMA and HB donor were reduced to 2 (entry 16, Table 5). The product was isolated in lower yields when DMA–CCl_4 was employed (entry 17, Table 5), while none of CH_2Br_2, NBS and $BrCH_2CN$ practically led to product (entries 18-20, Table 5).

Table 5. Photochemical coupling of Z-L-Phe-OH (**1**) to HCl.H-Gly-OEt (**2**) using DMAP or DMA and various HB donors.[a]



1 2 3

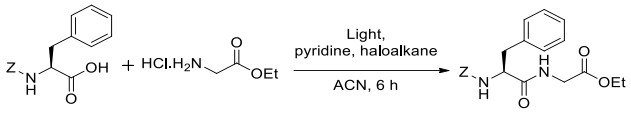
Entry	**Haloalkane**	**HB acceptor**	**Light**	**Yield (%)[b]**
1[c]	$BrCCl_3$	DMAP	370 nm	69
2[c,d]	$BrCCl_3$	DMAP	370 nm	16
3	**$BrCCl_3$**	**DMAP**	**370 nm**	**75**
4	$BrCCl_3$	DMAP	sunlight	67
5	**CBr_4**	**DMAP**	**370 nm**	**71**
6	CBr_4	DMAP	sunlight	59
7	CCl_4	DMAP	370 nm	65
8	CH_2Br_2	DMAP	370 nm	10
9	NBS	DMAP	370 nm	11
10	$BrCH_2CN$	DMAP	370 nm	1
11[c]	$BrCCl_3$	DMA	370 nm	50
12	**$BrCCl_3$**	**DMA**	**370 nm**	**77**
13	$BrCCl_3$	DMA	sunlight	69
14	CBr_4	DMA	370 nm	62
15	CBr_4	DMA	sunlight	48
16[e]	CBr_4	DMA	370 nm	15
17	CCl_4	DMA	370 nm	42
18	CH_2Br_2	DMA	370 nm	0
19	NBS	DMA	370 nm	5
20	$BrCH_2CN$	DMA	370 nm	0

[a] Reaction conditions: **1** (0.28 mmol), **2** (0.56 mmol), DMAP or DMA (2.80 mmol), haloalkane (2.80 mmol), ACN (4.25 mL), light irradiation at r.t.. [b] Yield of **3** after isolation by column chromatography. [c] DCE (4.25 mL) was used instead of ACN. [d] 2 equivalents of DMAP and $BrCCl_3$ were employed. [e] 2 equivalents of DMA and CBr_4 were employed.

Next, the combination of pyridine with various HB donors was studied (Table 6 and Table S3). First, ten equivalents of pyridine and $BrCCl_3$ or CBr_4 or CCl_4 and two equivalents of the amine component were used (entries 1-4, Table 6). The coupling product was isolated in high yield using CBr_4 (83%, entry 3, Table 6) after 6 h of LED irradiation at 370 nm, while lower yield was found using $BrCCl_3$ and practically no reaction was observed using CCl_4 under the same conditions (entries 1 and 2, Table 6). Sunlight was proven ineffective, leading to low yield (entry 4, Table 6). Gratifyingly, 80% yield was achieved when the equivalents of pyridine and CBr_4 were reduced to 5 (Table S3).[17] The yield remained high (78%), even when 2 equivalents of pyridine and CBr_4 were used (entry 5, Table 6), indicating that super-stoichiometric quantities of amine–organohalogen components may be overcome. Under dark, no product was obtained (entry 6, Table 6), while irradiation at higher wavelength resulted in slightly lower yield (entry 7, Table 6). As in the case of DMAP and DMA, the use of CH_2Br_2 did not lead to product (entry 8, Table 6). Efforts to modify the ratio of pyridine, CBr_4 and amine component led to lower yields (entries 9-11, Table 6).

Our detailed study of various HB donors and acceptors pairs revealed that indeed various pairs enable the amidation reaction. However, pyridine–CBr_4 stands out as a very efficient combination for an amidation reaction, under LED 370 nm irradiation in ACN, bypassing the need for super-stoichiometric quantities and leading to the highest yield of the desired product. To explore the substrate scope of this new photochemical

Table 6. Optimization of the photochemical coupling of Z-L-Phe-OH (**1**) to HCl.Gly-OEt (**2**) using pyridine and various halomethanes.[a]



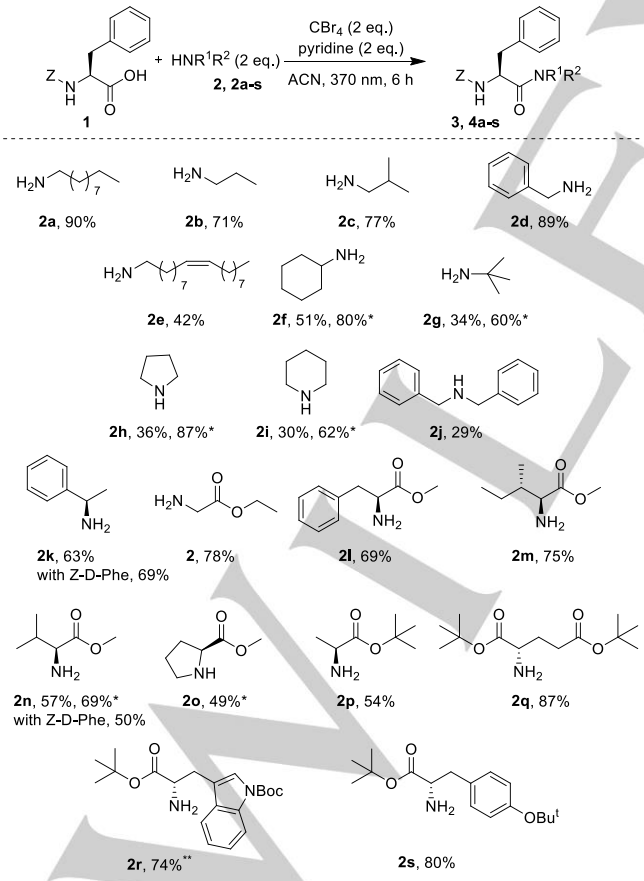
1 2 3

Entry	Haloalkane (eq.)	Pyridine (eq.)	Light	Yield (%)[b]
1	$BrCCl_3$, 10	10	370 nm	47
2	CCl_4, 10	10	370 nm	1
3	**CBr_4 10**	**10**	**370 nm**	**83**
4	CBr_4 10	10	sunlight	25
5	**CBr_4, 2**	**2**	**370 nm**	**78**
6	CBr_4, 2	2	dark	0
7	CBr_4, 2	2	390 nm	77
8	CH_2Br_2,10	10	370 nm	1
9[c]	CBr_4, 2	2	370 nm	71
10[d]	CBr_4, 2	2	370 nm	54
11	CBr_4,1	2	370 nm	59

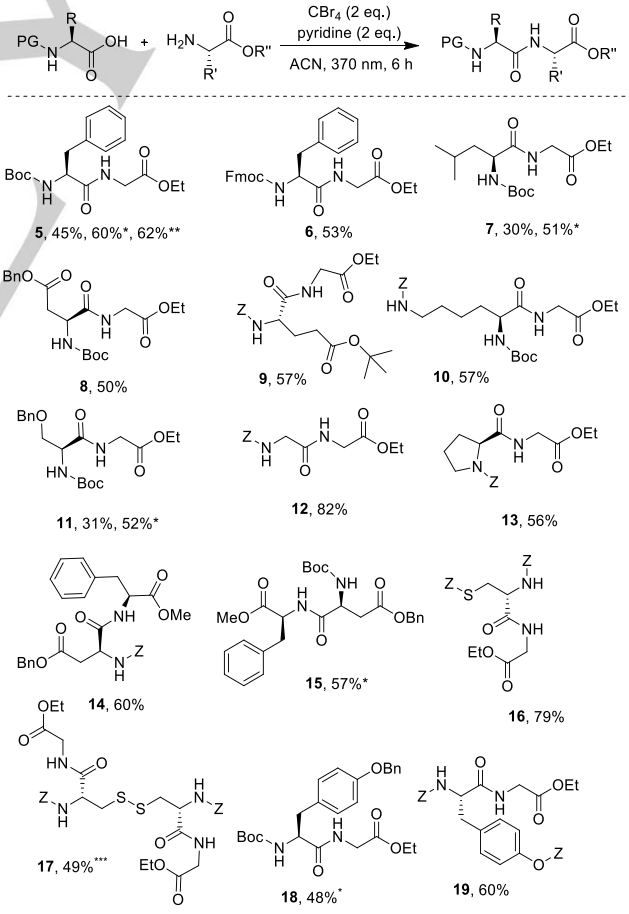
[a] Reaction conditions: **1** (0.28 mmol), **2** (0.56 mmol), pyridine, haloalkane, ACN (4.25 mL), light irradiation at r.t. [b] Yield of **3** after isolation by column chromatography. [c] 1.5 equivalent of **2**. [d] 1 equivalent of **2**.

protocol, we studied the coupling of Z-L-phenylalanine (**1**) to various amine components and the results are summarized in Scheme 2. Aliphatic saturated amines **2a-c**, as well as benzylamine (**2d**), coupled in high to excellent yields (71-90%). The product of coupling to oleyl amine (**2e**) was isolated in 42% yield, accompanied by addition products to the double bond, indicating that unsaturated compounds have limitations. Primary amines, such as **2f** and **2g**, on secondary or tertiary substituted carbon atoms, required a higher pyridine–CBr_4 ratio (5 equivalents) to reach 60-80% coupling yields. Secondary amines, such as pyrrolidine (**2h**) and piperidine (**2i**), afforded the coupling products in high to excellent yields, but a higher pyridine–CBr_4 ratio was required. Dibenzylamine (**2j**) led to lower yield. Chiral amine **2k** coupled well with both Z-L-Phe-OH or Z-D-Phe-OH. Coupling of a variety of C-protected amino acids **2** and **2l-s** (methyl, ethyl or *tert*-butyl esters) provided the products in moderate to excellent yields (54-87%). In the case of the sterically hindered valine (**2n**) or the secondary amine proline (**2o**), a higher pyridine–CBr_4 ratio may increase the yield. HPLC analysis of the coupling products of Z-L-Phe-OH or Z-D-Phe-OH to α-(*R*)-methyl benzylamine or methyl L-valinate, using a chiral column, showed that the light-mediated coupling protocol is free of epimerization.[17]

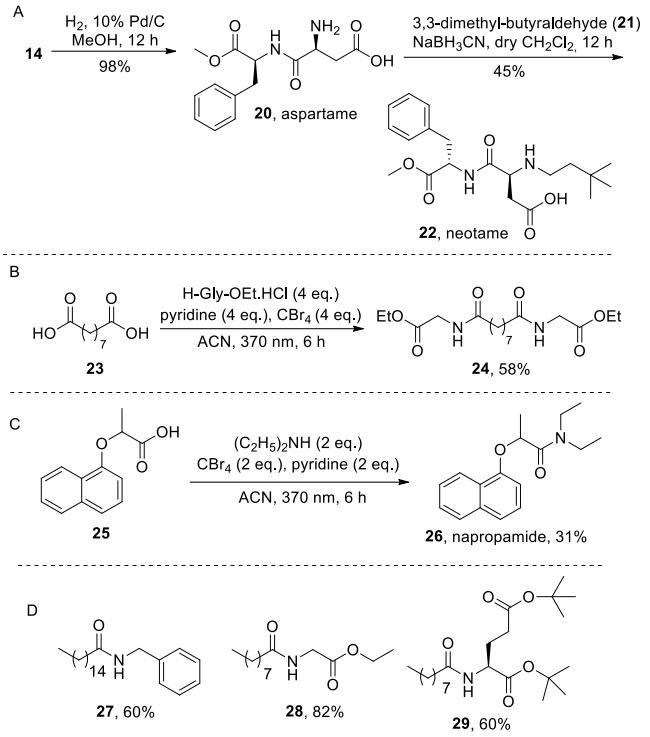
Then, we focused on the synthesis of dipeptides and the results are summarized in Scheme 3. Various commonly used in peptide synthesis amino protecting groups (benzyloxycarbonyl, Z, *tert*-butoxycarbonyl, Boc, and fluorenylmethyloxycarbonyl, Fmoc) and carboxy protecting groups (methyl, ethyl, benzyl, *tert*-butyl) were found compatible with this photochemical protocol, affording the dipeptides in yields ranging from 48-82%. In general, the yield of the coupling reaction may increase, if the pyridine–CBr_4 ratio is increased.



Scheme 2. Light-mediated coupling of Z-Phe-OH to various amine components using pyridine–CBr_4: Acid (0.28 mmol), amine (0.56 mmol), pyridine (0.56 mmol, 0.05 mL) and CBr_4 (0.56 mmol, 186 mg) in ACN (4.2 mL). * 5 eq. pyridine, 5 eq. CBr_4. ** 3 eq. pyridine.



Scheme 3. Light-mediated synthesis of dipeptides using pyridine–CBr_4: Acid (0.28 mmol), amine (0.56 mmol), pyridine (0.56 mmol, 0.05 mL) and CBr_4 (0.56 mmol, 186 mg) in ACN (4.2 mL). * 3 eq. pyridine. ** 4 eq. pyridine. *** 4 eq. pyridine, 4 eq. amine, 4 eq. CBr_4.



Scheme 4. Applications of the light-mediated pyridine–CBr_4 protocol for the synthesis of industrially interesting compounds and bioactive compounds: A. Artificial sweeteners aspartame and neotame, B. Azeloyl diglycinate, C. Napropamide, D. Macamide and fatty acid acyls.

Our photochemical protocol was further applied for the synthesis of industrially interesting products (Scheme 4). Aspartame (**20**) and neotame (**22**) are synthetic sweeteners, which are widely used in food industry, for example in refreshments, yogurts, lactic beverages, desserts, etc, and are produced in thousand tons annually.[22] Photochemical coupling of Z-Asp(OBn)-OH to H-Phe-OMe provided dipeptide **14** in 60% yield (Scheme 3), which after hydrogenation afforded aspartame **20** in 98% yield and subsequently neotame **22** after reductive amination with 3,3-dimethylbutyraldehyde (**21**) (Scheme 4, A). Azeloyl diglycinate, in the form of its potassium salt, finds use in cosmetics, exhibiting sebostatic and whitening action and offering a moisturizing effect, due to glycine.[23] Azelaic acid **23** was coupled to H-Gly-OEt, affording **24** in 58% yield (Scheme 4, B). Napropamide belongs to the amide herbicide family, and in its racemic form is widely used for pre-emergence control of annual grasses and broad-leaved weeds in many crops.[24] Coupling of **25** to diethylamine produced **26** in low yield (Scheme 4, C). Macamides are a unique class of long chain fatty acid *N*-benzylamides, constituting the major bioactive compounds of Maca, exhibiting fertility-enhancing, neuroprotective and neuro-modulatory, anti-fatigue and anti-osteoporosis activities.[25] Fatty acid acyls constitute an important family of endogenous signaling molecules that may regulate pain and inflammation.[26] Photochemical coupling of palmitic acid and pelargonic acid to benzylamine and amino acid esters, respectively, afforded palmitoyl benzylamide (**27**) and conjugates **28** and **29** in 60%-82% yields (Scheme 4, D).

The mechanism of the UVA-mediated coupling using pyridine–CBr_4 was studied by direct infusion−high resolution mass spectrometry (DI−HRMS). DI−HRMS finds interesting applications in non-targeted metabolomics as an alternative approach to chromatography−MS-based techniques.[27] We have successfully employed DI−HRMS for the elucidation of organic reaction mechanisms,[13d,28] because it offers a rapid and simplified approach, avoiding time-consuming chromatography and possible decomposition of sensitive to solvents analytes. Selected data of the HRMS analysis for the coupling of Z-Phe-OH to H-Gly-OEt utilizing pyridine–CBr_4 under LED 370 nm irradiation are depicted in Figure 3. Details on the mechanistic studies by DI−HRMS are described in the Supporting information.[17]

We begun the DI−HRMS mechanistic investigation, studying the interaction of pyridine with CBr_4 after irradiation at 370 nm. Upon such an irradiation, intermediate **I** (Scheme 5) was generated, whose cationic species was clearly observed by HRMS (Figure 3, B).[17] In addition, an ion corresponding to pyridine *N*-oxide **II** was formed (Figure 3, B). When a mixture of Z-Phe-OH, pyridine and CBr_4 was irradiated at 370 nm, intermediates **I** and **II** were also observed. However, monitoring the full scan spectrum of the reaction mixture, our attention was captured by an ion observed at *m/z* 603.2091 (Figure 3, A). This ion was recorded from the beginning of the reaction (30 min) and was present during the entire time course of the study (up to 3 h). Using Smart Formula application of Data Analysis from Bruker Daltonics (version 4.1), this measured exact mass was found to correspond to $C_{34}H_{32}N_2NaO_7^+$ (excellent mass error and isotopic fit) (Figure 3, A), which may be attributed to the formation of the symmetric anhydride of Z-Phe-OH (intermediate **V**). To explain the generation of such an intermediate, we searched for possible activated forms of Z-Phe-OH. Indeed, ions which may be attributed to the formation of two activated intermediates of Z-Phe-OH were detected. The most intense peak may correspond to the acyloxy pyridinium intermediate **III** (Figure 3, B), which may play a role as the active ester of Z-Phe-OH with pyridine *N*-oxide. In addition, an ion that may correspond to a mixed anhydride of Z-Phe-OH with hypobromous acid (intermediate **IV**) was observed (Figure 3, B). Both of them may generate the symmetric anhydride **V** upon their reaction with the carboxylate anion. In addition, a low abundancy ion, which may be attributed to an acyl pyridinium ion of Z-Phe-OH (intermediate **VI**) was recorded.[17] When a mixture of Z-Phe-OH, pyridine and CBr_4 was stirred under dark, none of the ions corresponding to intermediates **III**, **IV** and **V** were observed. Next, we monitored the mixture of the coupling reaction (Z-Phe-OH, H-Gly-OEt, pyridine, CBr_4) upon irradiation at 370 nm. Ions corresponding to the symmetric anhydride **V**, as well all the activated intermediates of Z-Phe-OH were recorded,[17] providing clear experimental evidence for a multiple activation mode of the carboxylic acid component. Our attempts to isolate the symmetric anhydride of Z-Phe-OH from the reaction mixture failed. However, we succeeded to isolate palmitic anhydride, when a mixture of palmitic acid, pyridine and CBr_4 was irradiated at 370 nm for 3 h.[17]

Taking all the above data into account, a plausible mechanism may be proposed, as shown in Scheme 5. Initially, halogen bonding between pyridine and CBr_4 occurs. After

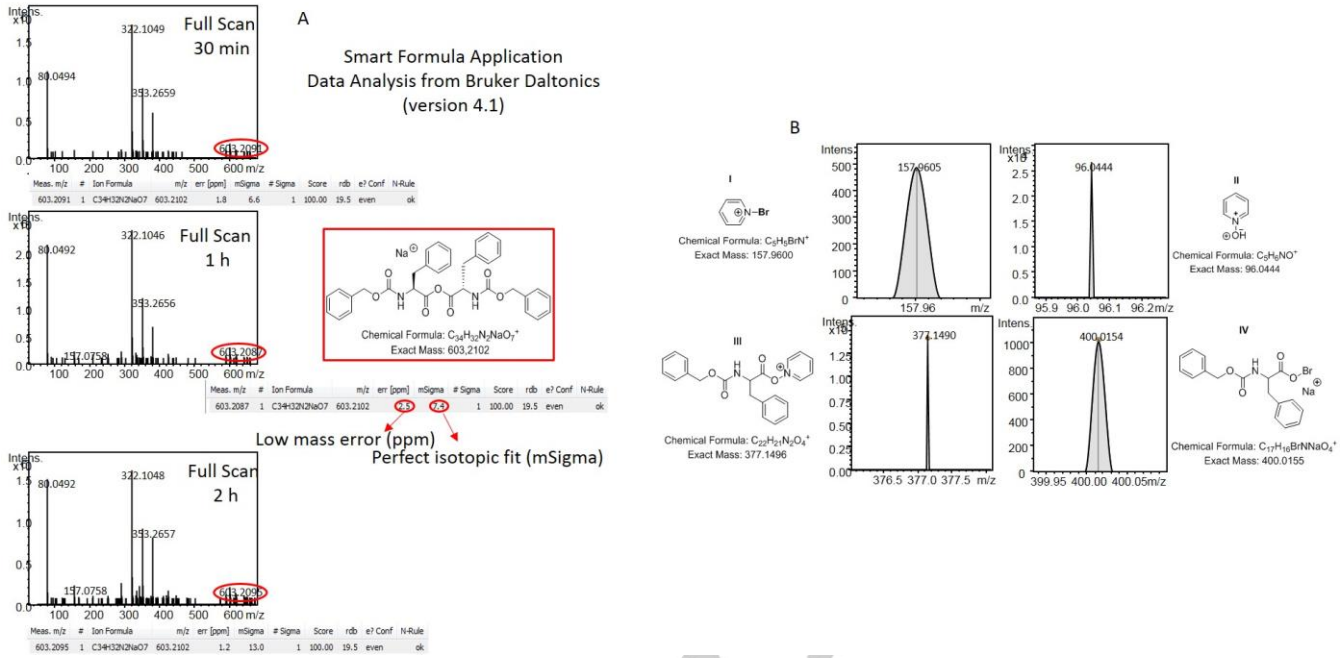
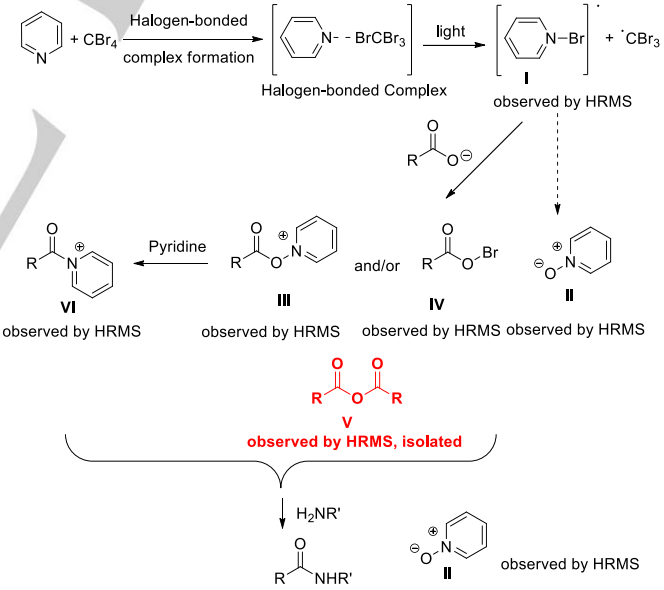


Figure 3. A. Monitoring of activation of Z-Phe-OH by pyridine and CBr_4 under LED 370 nm irradiation. Full scan HRMS spectra verifying the generation of symmetric anhydride (*m/z* 603.2102), B. Selected extracted ion chromatograms indicating the formation of various intermediates during the photochemical coupling of Z-Phe-OEt to H-Gly-OEt.

irradiation of the coupling reaction mixture, intermediate **I** is formed. Then, various activated carboxylic acid intermediates are generated (symmetric anhydride **V**, active ester with pyridine oxide **III**, mixed anhydride with hypobromous acid **IV**), which may lead to the coupling product after the successful nucleophilic attack of the amine component. The symmetric anhydrides are well known activated intermediates for use in amide and peptide coupling,[29] and this may be the major pathway in the present photochemical protocol, leading to coupling product. Based on the high abundancy of the ion corresponding to the acyloxy pyridinium intermediate **III**, we suggest that this intermediate may also play a key-role. 4-(Dimethylamino)pyridine *N*-oxide (DMAPO) has been described as an effective catalyst in peptide coupling reactions.[30a] In addition, such an activated derivative has been synthesized from DMAPO and cinnamoyl chloride and successfully used for coupling with an amine.[30b] In our photochemical protocol, we propose that the reactive acyloxy pyridinium intermediate is generated *in situ* as a result of the pyridine–CBr_4 mixture irradiation. To our knowledge, this is the first time such an activated intermediate based on pyridine *N*-oxide is observed and proposed as an effective intermediate for the amide bond formation. In parallel, a mixed anhydride of Z-Phe-OH with hypobromous acid (intermediate **IV**) may lead to the coupling product after attack of the amine component. Mixed anhydrides of carboxylic acids with inorganic acids have been studied for the coupling reaction at older times,[31] but at the end mixed carbonic anhydrides have been extensively used in peptide synthesis. Again, to our knowledge this is the first time a mixed anhydride of a protected amino acid with hypobromous acid is



Scheme 5. HRMS-guided proposed mechanism for the photochemical coupling of carboxylic acid RCOOH to amine R'NH_2 using pyridine–CBr_4.

proposed as effective intermediate for amidation reaction. Finally, the acyl pyridinium intermediate **VI** may be formed, leading to the final product after attack by the amine.

To sum up, careful monitoring and examination of the HRMS spectra suggested the generation of unprecedented carboxylate intermediates. The symmetric anhydride of palmitic

acid was isolated, confirming that this intermediate play a key-role in this light-mediated protocol.[17] Thus, a thorough study involving UV-Vis, NMR, DFT calculations, DI−HRMS and experimental data revealed a new activation process for the coupling of carboxylic acids with amines, employing a low reagent ratio of pyridine–CBr_4 (2 equivalents). This present protocol significantly differs from the procedure introduced by Szpilman *et al.*,[10b] not only in the reaction mechanism, but also in reagent stoichiometry. Szpilman *et al.* demonstrated that DMAP–$BrCCl_3$ is a unique couple of CTC in DCE that when used in super-stoichiometric amounts (10 equivalents) is able to afford amide bond formation under sunlight, while postulated the generation of a hemiaminal ester of carboxylic acid via iminium salt formation (distinctively different than the species presented in the present study) as the active intermediate that drives the reaction.[10b] Herein, we demonstrate that various pairs of HB donors and acceptors can form HBCs that can promote the amide bond formation under 370 nm LED irradiation or sunlight. The use of pyridine–CBr_4 stands out and can overcome the necessity for super-stoichiometric amounts of reagents, working equally well when only two equivalents are employed. Extended spectroscopic and theoretical studies revealed the complicated nature of the reaction mechanism, which significantly differs in our protocol (different active intermediates are involved) and this is possibly the reason that lowering the amount of the reagents is feasible.

Conclusion

In conclusion, the detailed study of several pairs of amines and organohalogen sources revealed that various pairs may be used for a photochemical amidation reaction under either UVA or sunlight. Inexpensive pyridine–CBr_4 was identified as an efficient agent to perform amide bond formation reactions under LED 370 nm irradiation, avoiding super-stoichiometric quantities. The widely used amino protecting groups (Z, Boc, Fmoc) and carboxy protecting groups (methyl, ethyl, benzyl, *tert*-butyl) are compatible with this photochemical protocol. Applications of the new photochemical protocol for the synthesis of industrially interesting products and bioactive compounds were demonstrated. DI−HRMS studies shed light on the mechanism of the reaction, suggesting the light-mediated formation of a symmetric anhydride, an active ester of the carboxylic acid with pyridine *N*-oxide and a mixed anhydride between the carboxylic acid and hypobromous acid as the reactive intermediates. Thus, a novel efficient and low-cost photochemical protocol for the amide bond formation is demonstrated, uncovering the possibility of novel activation mode of a carboxylic acid under photoactivation of the pyridine–CBr_4 mixture.

Experimental Section

In a 25 mL Schlenk tube equipped with a PTFE-coated stirring bar, the appropriate acid (0.28 mmol), the amine (0.56 mmol), pyridine (0.56 mmol, 0.05 mL) and CBr_4 (0.56 mmol, 186 mg) along with ACN (4.2 mL, HPLC grade) were added. The reaction mixture was stirred under light irradiation (Kessil lamps 370 nm) for 6 h. Then, the solvent was removed *in vacuo* and the crude reaction mixture was treated with aqueous citric acid 10% (10 mL), before it was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL), aqueous $NaHCO_3$ (10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The desired product was purified by column chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: amide bond formation • DFT calculations • halogen bonding • light-mediated chemistry • peptides

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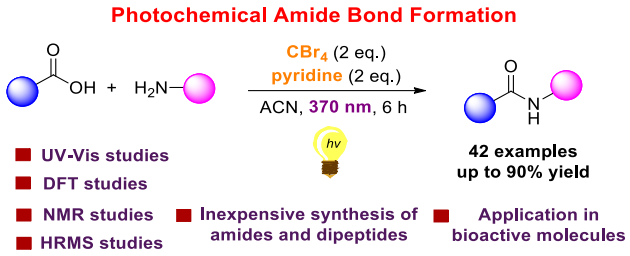

A UVA-light-mediated synthesis of amides from carboxylic acids and amines or amino acids is presented, taking advantage of a novel photoactivation mode using pyridine-CBr_4. Mechanistic studies by DI−HRMS provide experimental evidence for the formation of various intermediates. Application in the synthesis of industrially interesting or bioactive compounds was demonstrated.

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