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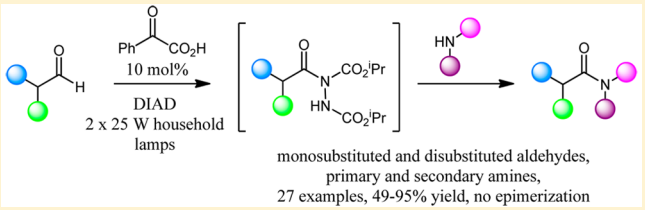
One-Pot Amide Bond Formation from Aldehydes and Amines via a Photoorganocatalytic Activation of Aldehydes

Giorgos N. Papadopoulos and Christoforos G. Kokotos*

Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodestrian University of Athens, Panepistimiopolis 15771, Athens, Greece

Supporting Information

ABSTRACT: A mild, one-pot, and environmentally friendly synthesis of amides from aldehydes and amines is described. Initially, a photoorganocatalytic reaction of aldehydes with diisopropyl azodicarboxylate leads to an intermediate carbonyl imide, which can react with a variety of amines to afford the desired amides. The initial visible light-mediated activation of a variety of monosubstituted or disubstituted aldehydes is usually fast, occurring in a few hours. Following the photocatalytic reaction, addition of the primary amine at room temperature or the secondary amine at elevated temperatures leads to the corresponding amide from moderate to excellent yields without epimerization. This methodology was applied in the synthesis of Moclobemide, a drug against depression and social anxiety.



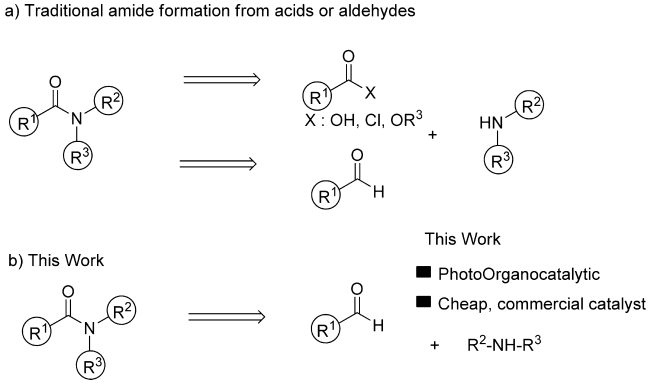
INTRODUCTION

Amide bond constitutes a fundamental functional group in organic and biological chemistry.[1] Since it can be found in natural products, polymers and pharmaceuticals (>25% of known medicine possess an amide bond),[1,2] a variety of approaches have been designed for its synthesis. Traditionally, a carboxylic acid and an amine are coupled to form an amide bond, although this reaction requires very high temperature (>180 °C) to overcome salt formation. To this end, a variety of coupling reagents[3] have been developed for the activation of the carboxylic acid toward the nucleophilic attack of the amine, but usually suffer from copious amounts of waste (Scheme 1). Another popular approach has been the use of uronium or phosphonium reagents.[3] In order to solve the problems of waste, researchers have developed a number of nonmetal catalysts for the synthesis of amides from carboxylic acids and amines, mainly based on boronic acids.[4] In addition, labile substrates or difficulty in certain classes of substrates have led to development of alternative catalytic methods.[5]

An alternative choice of reagents leading to amide bonds has been the coupling of an aldehyde with amines. Initially, oxidative metal-catalyzed processes were developed, mainly employing Cu-based catalysts,[6] while Milstein and co-workers pioneered the area of dehydrogenative acylation utilizing ruthenium-pincer complexes producing hydrogen gas as the only byproduct.[7] In order to avoid metal-based catalysts, a number of organocatalytic approaches have come forward,[8] where mainly NHC-catalyzed processes play a dominant role.[9] An alternative approach has been the *in situ* generation of an active N−Cl amine, which can be directly coupled with an aldehyde leading to the desired amide bond.[10] Finally, very recently, radical routes,[11] including photocatalytic alternatives, have been presented.[12]

We have recently diverted our scientific focus from organocatalysis[13] to photoorganocatalysis.[14] In that contribution, our experience in activated ketone chemistry[15,16] was combined with photocatalysis[17] to present a photoorganocatalytic hydroacylation of dialkyl azodicarboxylates.[14] There, the acyl hydrazide product could be coupled to an amine to lead to an amide.[11a,f,14] In this contribution, we present the evolution of this photoorganocatalytic process into an one-pot protocol for the synthesis of amides.

Scheme 1. Synthetic Approaches for the Synthesis of Amides



RESULTS AND DISCUSSION

In our previously developed photoorganocatalytic reaction, phenylglyoxylic acid was found to be the most efficient

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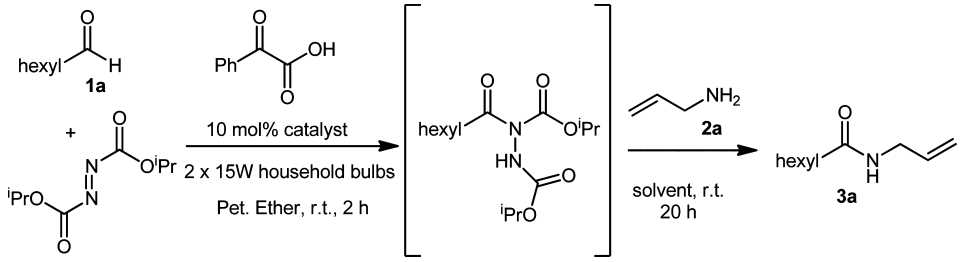
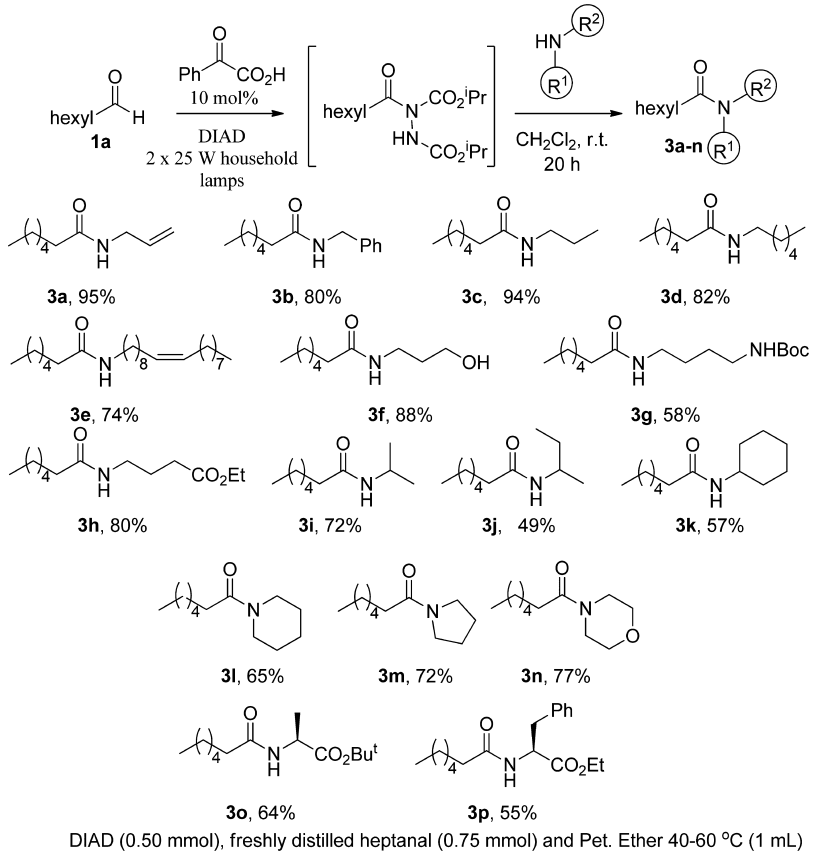
Table 1. One-pot Protocol for the Synthesis of Amides from Aldehydes



entry	conditions	yield (%)[a]
1	allylamine (1.5 equiv), CH_2Cl_2, r.t.	95
2	allylamine (1.1 equiv), CH_2Cl_2, r.t.	69
3	allylamine (1.5 equiv), $CHCl_3$, r.t.	84
4	allylamine (1.5 equiv), EtOAc, r.t.	73
5	allylamine (1.5 equiv), MeCN, r.t.	61

[a]Isolated yield, diisopropyl azodicarboxylate (0.50 mmol), freshly distilled or prepared aldehyde (0.75 mmol), and pet. ether 40−60 °C (1 mL).

Scheme 2. One-Pot Photoorganocatalytic Synthesis of Amides—Amine Substrate Scope



DIAD (0.50 mmol), freshly distilled heptanal (0.75 mmol) and Pet. Ether 40-60 °C (1 mL)

photoorganocatalyst among the activated ketones tested.[14] We were intrigued by the possibility of these acyl-imides to act as linchpins in a variety of transformations. Very recently, Caddick and co-workers suggested that acyl-imides, similarly to Weinreb amides, react with organometallic reagents to produce ketones.[18] In that contribution, preparation and isolation of acyl hydrazides was necessary and then were utilized for the ketone synthesis. Believing in the reactivity of these acyl hydrazides as activated acyl equivalents, we were interested in producing a one-pot protocol, which appears to be more attractive, since no intermediate purifications are required. At the beginning, phenylglyoxylic acid (10 mol%) was employed in the reaction between heptanal (**1a**) with di-isopropyl azodicarboxylate (DIAD) in petroleum ether (pet. ether) as the photocatalyst (for reaction setup, see Supporting Information). Complete decolorization of the reaction vessel signals reaction completion (2 h). Direct addition of allylamine (**2a**) led to an excellent yield of amide **3a** (entry 1, Table 1). Dilution of the reaction mixture was performed with dichloromethane, but it was not used as the solvent for the photoorganocatalytic step, since it requires longer reaction time to reach completion.[14] Lower amounts of allylamine (1.1 equiv) led to decreased yield (entry 2, Table 1). Other solvents led to lower isolated yields (entries 3−5, Table 1).

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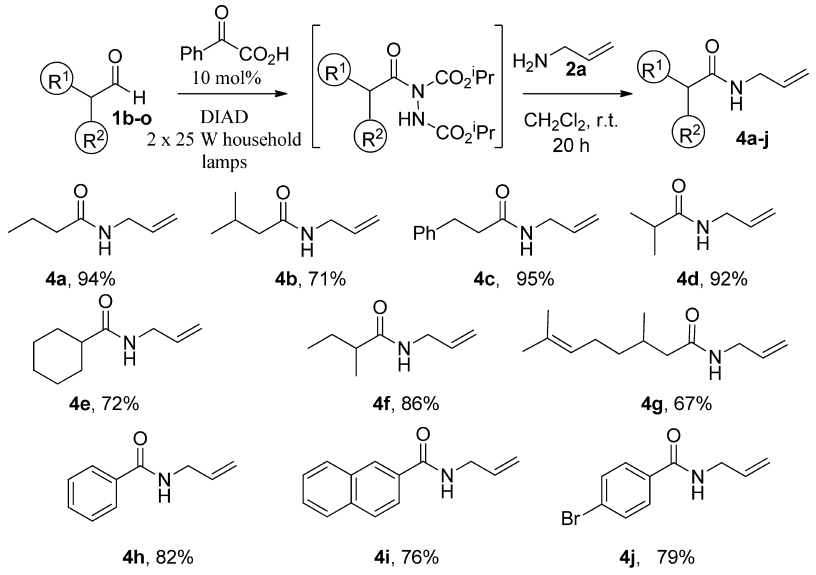
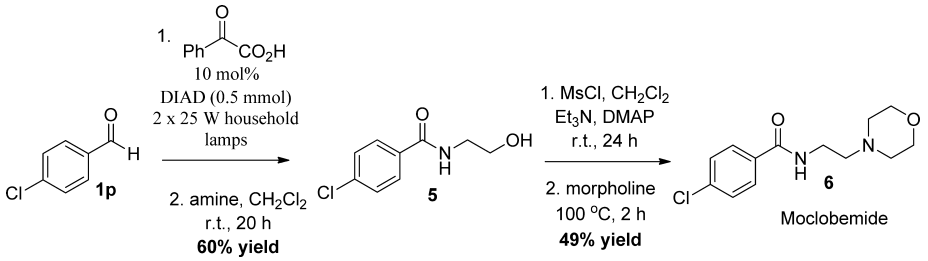
Scheme 3. One-Pot Photoorganocatalytic Synthesis of Amides—Aldehyde Substrate Scope



Scheme 4. Synthesis of Moclobemide



Once the optimum reaction conditions for the one-pot photoorganocatalytic synthesis of amides were identified, we explored the substrate scope (Scheme 2). Initially, heptanal (**1a**) reacted with a plethora of primary or secondary amines to afford amides **3a−p**.

Linear primary amines were initially employed leading to the corresponding amides **3a−e** in high yields. Terminal olefins, disubstituted double bonds, and aromatic moieties can be utilized without affecting the resulting yield of the amide. Primary amines that bear other functional groups, such as a hydroxyl group, as well as protected amines or esters were also tolerated leading to products **3f−h**. Thus, this methodology could be employed for further manipulation of the product or amide couplings after deprotection. Primary amines on branched secondary aliphatic chains can be utilized with similar success (compounds **3i−k**). Secondary amines, like piperidine, pyrrolidine, and moproholine, were also used, leading to amides **3l−n** in good yield. It has to be noted that in most of these last cases, five equivalents of amine at elevated temperature had to be employed to get acceptable yields. Finally, the most important amide bond forming reaction is that employing amino acid derivatives. Thus, two protected amino acids, *tert*-butyl alaninate and methyl phenylalaninate, were coupled with heptanal leading to the amide products **3o** and **3p** in good yields. In the last case, the racemic methyl ester of phenylalanine was also employed to yield racemic **3p**. After separation of the enantiomers of racemic **3p** using an HPLC equipped with a chiral column, the potential epimerization of our protocol in **3p**, under the reaction conditions, was checked and proved to be negligible.[19] Overall, a green one-pot photoorganocatalytic process that affords amides from aldehydes was developed. In all cases, various amines were employed successfully leading to the desired amides in good to excellent yields.

Then, various aldehydes were employed (Scheme 3). Linear and branched aliphatic aldehydes were employed leading to amides **4a−c** in high yields. Aldehydes with branched aliphatic chains at the α-position to the carbonyl group, including cyclohexyl carboxaldehyde, can be utilized with similar success (compounds **4d−f**). Aldehydes with aliphatic side chains bearing double bonds led to the isolation of the amide **4g** in good yields. Finally, aromatic aldehydes were also utilized, leading to high yields of the product (compounds **4h−j**).

Since, this one-pot protocol provides a facile and concise route to amide bond formation, we envisaged its application in the synthesis of a molecule of pharmaceutical relevance. Moclobemide is a drug that is used against depression and social anxiety.[20] Starting from 4-chlorobenzaldehyde, amide **5** was synthesized in a single step in 60% yield, utilizing our one-pot photoorganocatalytic protocol (Scheme 4). Amide **5** was then converted to Moclobemide **6** by a substitution reaction in 49% yield.

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CONCLUSIONS

In conclusion, we describe a highly efficient, green one-pot photoorganocatalytic protocol for the transformation of aldehydes to amides. Phenylglyoxylic acid, which is cheap, is employed as the photoorganocatalyst. Low-cost common household lamps are utilized, bypassing the use of high-cost metal-based photocatalysts or expensive photocatalytic apparatus. A variety of aliphatic primary and secondary amines bearing different functionalities were converted to the corresponding amides in high to excellent yields. Amino acids can be coupled via their amino component with this method without the loss of stereochemical information. Furthermore, a number of linear or branched aliphatic and aromatic aldehydes could be employed. This process was applied in the synthesis of Moclobemide, a currently employed drug for the treatment of anxiety.

EXPERIMENTAL SECTION

General Remarks. Chromatographic purification of products was accomplished using forced-flow chromatography. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates. Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde, or potassium permanganate stains. Melting points were determined on a hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a LC-MS spectrometer. HRMS spectra (ESI) were recorded on QTOF spectrometer. ^{1}H and ^{13}C NMR spectra were recorded (200 and 50 MHz, respectively) and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal, br m = broad signal multiplet), coupling constant, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Chiral high-performance liquid chromatography (HPLC) analyses were performed using chiral AD-H column.

General Procedure A for the Synthesis of Amides. Phenyl glyoxylic acid (7.5 mg, 0.05 mmol) was placed in a normal glass tube followed by diisopropyl azodicarboxylate (101 mg, 0.50 mmol) and pet. ether 40−60 °C (1 mL). Freshly distilled or prepared aldehyde (0.75 mmol) was then added. The reaction mixture was left stirring under light irradiation (2 × 15W household lamps, see Supporting Information) at room temperature for 90 min to 48 h depending on the substrate. After the reaction was judged complete (decolorization of the reaction), a solution of amine (0.75 mmol) in dry DCM (1 mL) was added. The reaction mixture was stirred at room temperature for 24 h. The crude product was purified using flash column chromatography or alumina (pet. eth.-EtOAc or pet. eth.-acetone).

General Procedure B for the Synthesis of Amides. Phenyl glyoxylic acid (7.5 mg, 0.05 mmol) was placed in a normal glass tube followed by diisopropyl azodicarboxylate (101 mg, 0.50 mmol) and pet. ether 40−60 °C (1 mL). Freshly distilled or prepared aldehyde (0.75 mmol) was then added. The reaction mixture was left stirring under light irradiation (2 × 15W household lamps, see Supporting Information) at room temperature for 90 min to 48 h depending on the substrate. After the reaction was judged complete (decolorization of the reaction), a solution of amine (2.50 mmol) in dry DCM (1 mL) was added. The reaction mixture was stirred at 50 °C for 24 h. The crude product was purified using flash column chromatography or alumina (pet. eth.-EtOAc or pet. eth.-acetone).

*N-Allylheptanamide (**3a**).*[21] *Utilizing General Procedure A.* Colorless oil, 81 mg, 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.07 (1H, br s), 5.87−5.67 (1H, m), 5.23−4.95 (2H, m), 3.82 (2H, t, J = 5.6 Hz,), 2.15 (2H, t, J = 7.4 Hz), 1.65−1.50 (2H, m), 1.35−1.15 (6H, m,), 0.83 (3H, t, J = 6.4 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 173.2, 134.3, 115.9, 41.7, 36.6, 31.4, 28.9, 25.7, 22.4, 13.9; MS (ESI) m/z (%): 168 [M-H, (65)]$^-$.

*N-Benzylheptanamide (**3b**).*[22] *Utilizing General Procedure A.* Pale yellow solid, 88 mg, 80% yield; mp 50−52 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55−7.10 (5H, m), 6.25 (1H, br s), 4.45−4.32 (2H, m,), 2.25 (2H, t, J = 7.2 Hz), 1.82−1.55 (2H, m), 1.50−1.10 (6H, m), 0.87 (3H, t, J = 7.2 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 173.3, 138.2, 128.6, 127.7, 127.3, 43.5, 36.5, 31.4, 28.9, 25.7, 22.4, 14.0; MS (ESI) m/z (%): 218 [M-H, (72)]$^-$.

*N-Propylheptanamide (**3c**).*[23] *Utilizing General Procedure A.* Yellow oil, 80 mg, 94% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.04 (1H, br s), 3.20−3.07 (2H, m), 2.11 (2H, t, J = 7.2 Hz), 1.65−1.35 (4H, m), 1.35−1.05 (6H, m), 0.85 (3H, t, J = 7.3 Hz), 0.81 (3H, t, J = 6.7 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 173.3, 41.0, 36.7, 31.4, 28.9, 25.7, 22.7, 22.4, 13.9, 11.2; MS (ESI) m/z (%): 170 [M-H, (69)]$^-$.

*N-Hexylheptanamide (**3d**).*[22] *Utilizing General Procedure A.* White solid, 88 mg, 82% yield; mp 45−47 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.84 (1H, br s), 3.22 (2H, q, J = 6.6 Hz), 2.12 (2H, t, J = 6.5 Hz), 1.72−1.37 (4H, m), 1.32−1.08 (12H, m), 0.88−0.76 (6H, m); ^{13}C (50 MHz, $CDCl_3$): δ 173.1, 39.4, 36.8, 31.5, 31.4, 29.5, 28.9, 26.5, 25.8, 22.5, 22.4, 14.0, 13.9; MS (ESI) m/z (%): 212 [M-H, (57)]$^-$.

*(Z)-N-(Octadec-9-en-1-yl)heptanamide (**3e**). Utilizing General Procedure A.* White solid, 140 mg, 74% yield; mp 106−108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.68 (1H, br s), 5.35−5.25 (2H, m), 3.25- 3.12 (2H, m), 2.13 (2H, t, J = 7.3 Hz), 2.02−1.92 (4H, m), 1.65−1.45 (4H, m), 1.42−1.15 (28H, m), 0.90−0.77 (6H, m); ^{13}C (50 MHz, $CDCl_3$): δ 173.1, 129.9, 129.7, 39.4, 36.8, 31.8, 31.5, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 27.1, 26.9, 25.8, 22.6, 22.5, 14.1, 14.0; HRMS exact mass calculated for [M-H]$^-$ ($C_{25}H_{48}ON$)$^-$ requires m/z 378.3741, found 378.3744.

*N-(3-Hydroxypropyl)heptanamide (**3f**). Utilizing General Procedure A.* Yellow oil, 83 mg, 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.23 (1H, br s), 3.59 (2H, t, J = 5.7 Hz), 3.37 (2H, q, J = 6.2 Hz), 3.11 (1H, br s), 2.17 (2H, t, J = 7.5 Hz), 1.77−1.47 (4H, m), 1.45−1.15 (6H, m), 0.85 (3H, t, J = 6.5 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 174.7, 59.0, 36.6, 36.0, 32.2, 31.5, 28.9, 25.7, 22.4, 14.0; HRMS exact mass calculated for [M-H]$^-$ ($C_{10}H_{20}O_2N$)$^-$ requires m/z 186.1500, found 186.1501.

*tert-Butyl (4-heptanamidobutyl)carbamate (**3g**). Utilizing General Procedure A.* White solid, 87 mg, 58% yield; mp 60−62 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.15 (1H, br s), 4.80 (1H, br s), 3.35−2.94 (4H, m), 2.14 (2H, t, J = 7.2 Hz), 1.58−1.40 (6H, m), 1.36 (9H, s), 1.26−1.16 (6H, m), 0.86 (3H, t, J = 6.7 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 173.3, 156.1, 79.0, 40.0, 38.9, 36.6, 31.4, 28.8, 28.2, 27.4, 26.6, 25.7, 22.4, 13.9; HRMS exact mass calculated for [M-H]$^-$ ($C_{16}H_{31}O_3N_2$)$^-$ requires m/z 299.2340, found 299.2344.

*Ethyl 4-heptanamidobutanoate (**3h**). Utilizing General Procedure B.* Pale orange oil, 97 mg, 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.81 (1H, br s), 4.12 (2H, q, J = 7.1 Hz), 3.27 (2H, q, J = 6.5 Hz), 2.34 (2H, t, J = 7.2 Hz), 2.11 (2H, t, J = 7.2 Hz), 1.92−1.72 (2H, m), 1.67−1.47 (2H, m), 1.42−1.08 (9H, m), 0.86 (3H, t, J = 6.5 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 173.5, 173.3, 60.5, 38.9, 36.8, 31.7, 31.5, 28.9, 25.7, 24.6, 22.4, 14.1, 14.0; HRMS exact mass calculated for [M + H]$^+$ ($C_{13}H_{26}O_3N$)$^+$ requires m/z 244.1907, found 244.1909.

*N-Isopropylheptanamide (**3i**).*[24] *Utilizing General Procedure B.* Yellow oil, 62 mg, 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.57 (1H, br s), 4.05 (1H, hept, J = 6.6 Hz), 2.08 (2H, t, J = 7.9 Hz), 1.65−1.45 (2H, m), 1.40−1.15 (6H, m), 1.07 (6H, d, J = 6.6 Hz), 0.83 (3H, t, J = 5.7 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.2, 41.0, 37.0, 31.5, 28.8, 25.7, 22.7, 22.4, 13.9; MS (ESI) m/z (%): 170 [M-H, (68)]$^-$.

*N-(sec-Butyl)heptanamide (**3j**). Utilizing General Procedure B.* Colorless oil, 45 mg, 49% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.34 (1H, br s), 4.14−3.72 (1H, m), 2.11 (2H, t, J = 7.1 Hz), 1.85−1.52 (2H, m), 1.50−1.20 (8H, m), 1.07 (3H, d, t, J = 6.6 Hz), 0.96−0.78 (6H, m); ^{13}C (50 MHz, $CDCl_3$): δ 172.4, 46.3, 37.0, 31.5, 29.6, 28.9, 25.8, 22.5, 20.4, 14.0, 10.3; HRMS exact mass calculated for [M-H]$^-$ ($C_{11}H_{22}ON$)$^-$ requires m/z 184.1707, found 184.1708.

*N-Cyclohexylheptanamide (**3k**).*[25] *Utilizing General Procedure B.* Yellow solid, 60 mg, 57% yield; mp 69−71 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.40 (1H, br s), 3.90−3.65 (1H, m), 2.10 (2H, t, J = 7.3 Hz), 1.97−1.80 (2H, m), 1.77−1.50 (5H, m), 1.48−1.00 (11H, m),

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0.85 (3H, t, J = 6.3 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.2, 48.0, 37.1, 33.2, 31.5, 28.9, 25.8, 25.5, 24.8, 22.5, 14.0; MS (ESI) m/z (%): 210 [M-H, (63)]$^-$.

*1-(Piperidin-1-yl)heptan-1-one (**3l**).*[26] *Utilizing General Procedure B.* Yellow oil, 64 mg, 65% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.51 (2H, t, J = 5.7 Hz), 3.35 (2H, t, J = 5.9 Hz), 2.28 (2H, t, J = 5.8 Hz), 1.75−1.40 (7H, m), 1.27−1.12 (7H, m), 0.85 (3H, t, J = 6.1 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 171.5, 46.7, 42.5, 33.4, 31.6, 29.2, 26.5, 25.5, 25.4, 24.5, 22.5, 14.0; MS (ESI) m/z (%): 198 [M+H, (79)]$^+$.

*1-(Pyrrolidin-1-yl)heptan-1-one (**3m**).*[26] *Utilizing General Procedure B.* Brown oil, 66 mg, 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.50−3.24 (4H, m), 2.24 (2H, t, J = 5.8 Hz), 1.95−1.75 (4H, m), 1.65−1.50 (2H, m), 1.40−1.10 (6H, m), 0.85 (3H, t, J = 6.1 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.1, 46.8, 45.8, 35.1, 31.9, 29.4, 26.3, 25.1, 24.6, 22.8, 14.3; MS (ESI) m/z (%): 184 [M+H, (85)]$^+$.

*1-Morpholinoheptan-1-one (**3n**).*[26] *Utilizing General Procedure B.* Yellow oil, 77 mg, 77% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.75−3.52 (6H, m), 3.40 (2H, t, J = 4.9 Hz), 2.27 (2H, t, J = 7.3 Hz), 1.68−1.45 (2H, m), 1.35−1.10 (6H, m), 0.84 (3H, t, J = 6.3 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.1, 67.1, 66.9, 46.2, 42.0, 33.3, 31.8, 29.3, 25.4, 22.7, 14.2; MS (ESI) m/z (%): 200 [M+H, (77)]$^+$.

*(S)-tert-Butyl 2-heptanamidopropanoate (**3o**). Utilizing General Procedure B.* Colorless oil, 82 mg, 64% yield; $[\alpha]_D^{20}$ = +90.0 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.13 (1H, br s), 4.54−4.30 (1H, m), 2.14 (2H, t, J = 7.2 Hz), 1.74−1.52 (2H, m), 1.44 (9H, s), 1.32 (3H, d, J = 7.1 Hz), 1.25−1.10 (6H, m), 0.83 (3H, t, J = 6.5 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.5, 156.0, 81.9, 48.3, 35.6, 31.4, 28.8, 27.9, 25.5, 22.4, 18.7, 13.9; HRMS exact mass calculated for $[M-H]^-$ $(C_{14}H_{26}O_3N)^-$ requires m/z 256.1918, found 256.1923.

*(S)-Methyl 2-heptanamido-3-phenylpropanoate (**3p**). Utilizing General Procedure B.* Orange oil, 80 mg, 55% yield; 99% ee; $[\alpha]_D^{20}$ = −48.9 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40−6.95 (5H, m), 5.91 (1H, br d, J = 7.2 Hz), 5.05−4.72 (1H, m), 3.72 (3H, s), 3.25−2.95 (2H, m), 2.16 (2H, t, J = 7.5 Hz), 1.72−1.45 (2H, m), 1.40−1.07 (6H, m), 0.86 (3H, t, J = 6.3 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.7, 172.2, 135.8, 129.2, 128.5, 127.0, 52.8, 52.3, 37.8, 36.5, 31.4, 28.8, 25.5, 22.4, 14.0; HRMS exact mass calculated for $[M + H]^+$ $(C_{17}H_{26}O_3N)^+$ requires m/z 292.1907, found 292.1909; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 92:8, flow rate 1.0 mL/min, retention time: 12.52 [minor (R)] and 18.82 [minor (S)], 99% *ee*.

*N-Allylbutyramide (**4a**).*[27] *Utilizing General Procedure A.* Yellow oil, 66 mg, 94% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.02−5.64 (2H, m), 5.25−4.95 (2H, m), 3.95−3.70 (2H, m), 2.20−1.96 (2H, m), 1.79−1.69 (2H, m), 0.91 (3H, t, J = 6.6 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.5, 134.3, 116.1, 46.0, 41.7, 26.0, 22.3; MS (ESI) m/z (%): 140 [M-H, (68)]$^-$.

*N-Allyl-3-methylbutanamide (**4b**). Utilizing General Procedure A.* Yellow oil, 51 mg, 71% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.02−5.64 (2H, m), 5.25−4.95 (2H, m), 3.95−3.70 (2H, m), 2.20−1.86 (3H, m), 0.91 (6H, d, J = 6.0 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.5, 134.3, 116.1, 46.0, 41.7, 26.0, 22.3; HRMS exact mass calculated for $[M-H]^-$ $(C_8H_{14}ON)^-$ requires m/z 140.1086, found 140.1089.

*N-Allyl-3-phenylpropanamide (**4c**).*[28] *Utilizing General Procedure A.* Colorless oil, 90 mg, 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42−6.98 (5H, m), 6.05 (1H, br s), 5.87−5.60 (1H, m), 5.19−4.90 (2H, m), 3.90−3.60 (2H, m), 2.94 (2H, t, J = 7.7 Hz), 2.48 (2H, t, J = 7.7 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.0, 140.1, 134.0, 128.3, 128.2, 126.0, 116.0, 41.7, 38.1, 31.6; MS (ESI) m/z (%): 188 [M-H, (73)]$^-$.

*N-Allylisobutyramide (**4d**).*[29] *Utilizing General Procedure A.* Colorless oil, 58 mg, 92% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.00−5.70 (2H, m), 5.25- 5.00 (2H, m), 3.83 (2H, t, J = 5.6 Hz), 2.50−2.28 (1H, m), 1.12 (6H, d, J = 6.9 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 176.9, 134.3, 116.1, 41.7, 35.5, 19.6; MS (ESI) m/z (%): 126 [M-H, (59)]$^-$.

*N-Allylcyclohexanecarboxamide (**4e**).*[30] *Utilizing General Procedure A.* Colorless solid, 60 mg, 72% yield; mp 70−72 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.97−5.65 (2H, m), 5.32−5.00 (2H, m), 3.94−3.67 (2H, m), 2.25−1.92 (1H, m), 1.90−1.57 (5H, m), 1.52−1.02 (5H, m); ^{13}C (50 MHz, $CDCl_3$): δ 176.0, 134.4, 116.0, 45.4, 41.6, 29.6, 25.7, 21.9; MS (ESI) m/z (%): 166 [M-H, (71)]$^-$.

*N-Allyl-2-methylbutanamide (**4f**).*[31] *Utilizing General Procedure A.* Yellow oil, 61 mg, 86% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.05−5.65 (2H, m), 5.25−5.00 (2H, m), 4.00−3.72 (2H, m), 2.30−1.95 (1H, m), 1.79−1.53 (1H, m), 1.48−1.32 (1H, m), 1.11 (3H, d, J = 6.8 Hz), 0.85 (3H, t, J = 7.4 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 176.4, 134.4, 116.0, 43.1, 41.6, 27.2, 17.5, 11.9; MS (ESI) m/z (%): 140 [M-H, (67)]$^-$.

*N-Allyl-3,7-dimethyloct-6-enamide (**4g**).*[32] *Utilizing General Procedure B.* Orange solid, 70 mg, 67% yield; mp 96−98 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.98−5.58 (2H, m), 5.33−4.88 (3H, m), 3.88−3.70 (2H, m), 2.34−2.07 (1H, m), 2.05−1.85 (4H, m), 1.64 (3H, s), 1.56 (3H, s), 1.39−1.18 (2H, m), 0.90 (3H, d, J = 6.2 Hz); ^{13}C (50 MHz, $CDCl_3$): δ 172.4, 134.3, 131.4, 124.2, 116.1, 44.4, 41.8, 36.8, 30.1, 25.6, 25.4, 19.4, 17.6; MS (ESI) m/z (%): 208 [M-H, (77)]$^-$.

*N-Allylbenzamide (**4h**).*[33] *Utilizing General Procedure A.* Colorless oil, 66 mg, 82% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82−7.70 (2H, m), 7.45−7.20 (3H, m), 6.59−6.39 (1H, br s), 5.92−5.70 (1H, m), 5.20−5.00 (2H, m), 4.00−3.90 (2H, m); ^{13}C (50 MHz, $CDCl_3$): δ 167.5, 133.9, 131.1, 128.1, 126.7, 115.8, 42.1; MS (ESI) m/z (%): 160 [M-H, (67)]$^-$.

*N-Allylnaphthalen-2-amine (**4i**). Utilizing General Procedure A.* Brown solid, 81 mg, 76% yield; mp 96−98 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28 (1H, s), 7.90−7.72 (4H, m), 7.57−7.40 (2H, m), 6.85 (1H, br s), 6.05−5.80 (1H, m), 5.30−5.10 (2H, m), 4.20−3.90 (2H, m); ^{13}C (50 MHz, $CDCl_3$): δ 167.5, 134.6, 134.1, 132.4, 131.5, 128.8, 128.3, 127.6, 127.5, 127.4, 126.6, 123.5, 116.5, 42.5; HRMS exact mass calculated for $[M-H]^-$ $(C_{14}H_{12}ON)^-$ requires m/z 210.0924, found 210.0922.

*N-Allyl-4-bromobenzamide (**4j**).*[33] *Utilizing General Procedure A.* White solid, 95 mg, 79% yield; mp 92−94 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63 (2H, d, J = 8.1 Hz), 7.49 (2H, d, J = 8.1 Hz), 6.72 (1H, br s), 6.00−5.70 (1H, m), 5.30−5.05 (2H, m), 4.10−3.90 (2H, m); ^{13}C (50 MHz, $CDCl_3$): δ 166.4, 133.8, 133.1, 131.7, 128.6, 126.1, 116.7, 42.4; MS (ESI) m/z (%): 237 [M-H, (52)]$^-$.

*4-Chloro-N-(2-hydroxyethyl)benzamide (**5**).*[20b] *Utilizing General Procedure A.* White solid, 60 mg, 60% yield; mp 68−70 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.08 (1H, br t, J = 5.2 Hz), 3.73 (2H, t, J = 4.7 Hz), 3.60−3.45 (3H, m); ^{13}C (50 MHz, $CDCl_3$): δ 167.6, 137.9, 132.3, 128.7, 128.4, 61.7, 42.7; MS (ESI) m/z (%): 198 [M-H, (75)]$^-$.

*4-Chloro-N-(2-morpholinoethyl)benzamide (**6**).*[20b] To a stirring solution of 4-chloro-*N*-(2-hydroxyethyl)benzamide **5** (199 mg, 1.00 mmol) in dry dichloromethane (10 mL), Et_3N (0.42 mL, 3.00 mmol), DMAP (12 mg, 0.10 mmol), NaCl (175 mg, 3.00 mmol) and MsCl (0.23 mL, 3.00 mmol) were added and the reaction mixture was left stirring for 24 h at room temperature. The organic layer was washed with aq. 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried and the solvent was evaporated *in vacuo*. Morpholine (0.70 mL, 8.00 mmol) was added to the crude reaction mixture and was left stirring for 2 h at 100 °C. The crude mixture was purified using flash column chromatography CH_2Cl_2:MeOH 95:5 to afford Moclobemide **6**. White solid, 133 mg, 49% yield; mp 135−137 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 (2H, d, J = 8.6 Hz), 7.41 (2H, d, J = 8.6 Hz), 6.79 (1H, br s), 3.79−3.68 (4H, m), 3.57−3.45 (2H, m), 2.61 (2H, t, J = 6.1 Hz), 2.55−2.45 (4H, m); ^{13}C (50 MHz, $CDCl_3$): δ 166.2, 137.3, 132.7, 128.5, 128.2, 66.7, 58.7, 53.1, 36.0; MS (ESI) m/z (%): 267 [M-H, (71)]$^-$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00488.

Photochemical setup, NMR, and HPLC data (PDF)

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AUTHOR INFORMATION

Corresponding Author

* Tel: +30 210 7274281; E-mail: ckokotos@chem.uoa.gr.

Notes

The authors declare no competing financial interest.

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