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Article

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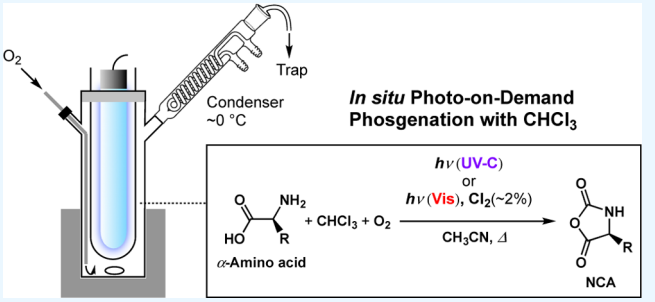
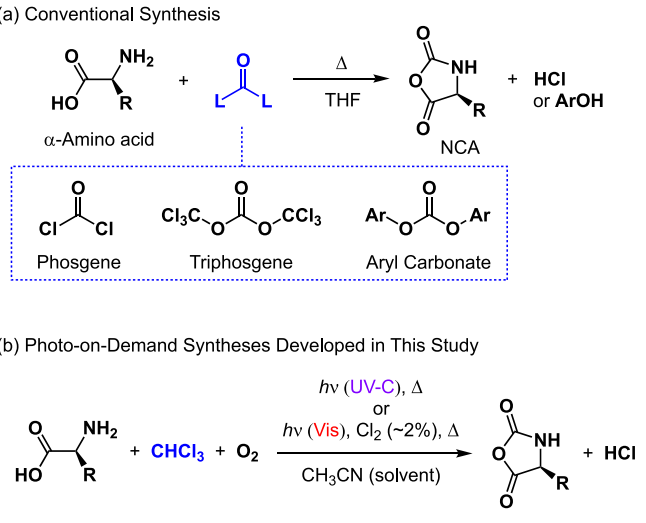
ABSTRACT: Amino acid *N*-carboxyanhydrides (NCAs) are conventionally synthesized from α-amino acids and phosgene. The present study reports in situ photo-on-demand phosgenation reactions of amino acids with $CHCl_3$ for synthesizing NCAs. A series of NCAs were obtained on a gram scale upon photoirradiation of a mixture solution of $CHCl_3$ and CH_3CN containing an amino acid at 60−70 °C under O_2 bubbling. This method presents a safe and convenient reaction controlled by light without special apparatuses and reagents.



INTRODUCTION

α-Amino acid *N*-carboxyanhydrides (NCAs), first discovered by Leuchs,[1] are widely used as building blocks for synthesizing artificial polypeptides, which have attracted increasing attention due to their versatile biomedical applications such as drug delivery, antibiotics, gene therapy, and tissue engineering.[2,3] They are conventionally synthesized from α-amino acids and phosgene ($COCl_2$) [Scheme 1a, phosgene].[4] However, since $COCl_2$ is a highly toxic gaseous compound at room temperature,[5] safer methods of using $COCl_2$ and exploration of phosgene substitutes have been important research subjects in the field of organic chemistry.

Scheme 1. Syntheses of Amino Acid NCAs: (a) Conventional Reactions and (b) New Reactions Developed in This Study



For safe use of $COCl_2$, bis(trichloromethyl)carbonate (BTC), generally called triphosgene, has been preferably used as the phosgene substitute in laboratory-scale syntheses.[6] BTC, which is a solid under standard conditions, allows in situ generation of $COCl_2$ in the solution through reactions with nucleophiles. An α-amino acid reacts with BTC to give a mixture of the corresponding NCA and its HCl salt (Scheme 1a, triphosgene).[7a] An organic base, which serves as both the nucleophile and HCl scavenger, accelerates the reaction to increase the yield of NCA. Recently, Lu and coworkers reported that epoxy compounds served as ultra-fast scavengers of HCl to allow assisted ring-closure and prevent acid-catalyzed decomposition of NCA under moist conditions.[8] Combined with flow chemistry, Fuse and coworkers demonstrated the conventional reactions with BTC that allow continuous production of NCAs while reducing the potential safety risks of using $COCl_2$.[9] However, recently, Cotarca and coworkers have reported that BTC also has high toxicity, and its vapor pressure is sufficiently high to easily attain toxic concentrations.[10] They suggested strict safety control when using BTC. Furthermore, there is a potential practical disadvantage in that the additives, both reacted and unreacted with HCl, generated by the reaction must be

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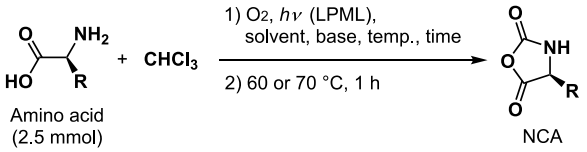
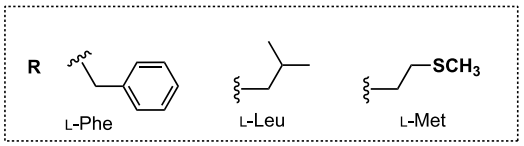
Table 1. Photochemical Syntheses of Amino Acid NCAs with UV Light





LPML : Low-Pressure Mercury Lamp

entry	amino acid	$CHCl_3$ (mL)	solvent (mL)	base (equiv)	temp. (°C)	time (h)	NCA yield (%)[c]
1A	L-Phe	30			20	2[a]	
1B	L-Phe	30			60	2[a]	23
1C	L-Phe	30		Py (2.6)	60	2[a]	45
1D	L-Phe	30		NMM (2.6)	60	2[a]	62
1E	L-Phe	15	CH_3CN 15		60	2[b]	48
1F	L-Phe	15	CH_3CN 15		70	2[b]	>99 (89)[d] [>99% ee][e]
1G	L-Phe	$CDCl_3$ 15	CH_3CN 15		70	2[b]	59
1H	L-Phe	7.5	CH_3CN 22.5		70	2[b]	84
1I	L-Phe·HCl (1.7 mmol)	15	CH_3CN 15		70	2[b]	70
2A	L-Leu	30			60	2[a]	11
2B	L-Leu	30		Py (2.6)	60	2[a]	40
2C	L-Leu	30		NMM (2.6)	60	2[a]	51
2D	L-Leu	15	CH_3CN 15		60	2[b]	41
2E	L-Leu	15	CH_3CN 15		70	2[b]	90 (85)[d] [>99% ee][e]
3A	L-Met	30			60	2[a]	11
3B	L-Met	30		Py (2.6)	60	2[a]	40
3C	L-Met	15	CH_3CN 15		60	2[b]	53
3D	L-Met	15	CH_3CN 15		70	2[b]	93 (52)[d] [99% ee][e]

[a]Repeated 5 min ON and 5 min OFF of photo-irradiation with LPML. [b]Repeated 5 min ON and 10 min OFF of photo-irradiation with LPML. [c]Yield determined by ^1H NMR analysis. [d]Isolated yield. [e]Enantiomeric excess determined by chiral HPLC analysis.

removed by post-purification processes. This increases the amount of waste, time, and cost of synthesis.

Some methods for synthesizing NCAs without using $COCl_2$ have been developed with NO gas and oxalyl chloride,[11] di-*tert*-butyltricarbonate,[12] cyanuric chloride,[13] and bisaryl carbonates (Scheme 1a, aryl carbonate).[14] Reactions with Boc-protected α-amino acids and *n*-propanephosphonic acid anhydride also allowed the synthesis of NCAs.[15] However, these reactions have not replaced the conventional synthetic method due to their low versatility, formation of side products, corrosiveness and toxicity of the reactants, complexity of the reaction, elaborate purification processes, and cost. Even after reducing the safety risk, the classical reaction with $COCl_2$ still has practical advantages. This background motivated us to develop an innovative synthetic method for NCAs with $CHCl_3$ capable of generating $COCl_2$ in situ by photo-irradiation.[16]

We previously reported that $CHCl_3$ underwent oxidative photochemical conversion to $COCl_2$ under exposure to UV light.[17] Contrarily, other chlorocarbons such as CCl_4 and CH_2Cl_2 produced less amounts of $COCl_2$ through similar photochemical reactions. The reaction with $CHCl_3$ could be applied to a variety of in situ phosgenation reactions like with BTC.[18−21] Compared with BTC, $CHCl_3$ is an inexpensive and more abundant compound capable of being used as a solvent. Further, the reaction allows photo-on-demand control of phosgenation reactions without using the chemical additives. Thus, the method with $CHCl_3$ has clear advantages in terms of cost and safety and can reduce possible side-reactions caused by the additives. For example, carbonate esters and their intermediate chloroformates were synthesized in high yields only upon irradiation by UV-C light of $CHCl_3$ solutions containing an alcohol with or without an organic base.[20] Furthermore, we recently reported that these photochemical reactions occurred with visible light in the presence of a small amount of Cl_2.[22] To cause the reactions, there were threshold concentrations of alcohol and base in the $CHCl_3$ solution (generally $[CHCl_3] \gg [base] > [alcohol]$). However, surprisingly, we found in this study that photochemical oxidation of $CHCl_3$ occurred even in the presence of a larger amount of CH_3CN, which can increase the solvent polarity. This finding made it possible to apply the photo-on-demand phosgenation reaction to the synthesis of NCAs, which are generally synthesized in relatively high-polarity solvents such as THF.[4,7−9] In the present study, we successfully synthesized a series of NCAs simply by photo-irradiation of a mixed solution of $CHCl_3$ and CH_3CN containing α-amino acids at 60−70 °C under O_2 bubbling (Scheme 1b).

RESULTS AND DISCUSSION

We have proposed a radical chain mechanism for the oxidative photochemical conversion of $CHCl_3$ to $COCl_2$.[17b] Initial C−Cl bond cleavage in $CHCl_3$ upon exposure to light generates $Cl^•$, which extracts hydrogen from another $CHCl_3$ molecule to produce $Cl_3C^•$. This radical then reacts with O_2 to give $COCl_2$

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with the regeneration of Cl$^{\bullet}$ to repeat the cycle. A low-pressure mercury lamp (LPML) emits UV-C light, mainly at 184.9 and 253.7 nm, and has relatively low electric power consumption compared with other lamps, including LEDs. This UV-C light causes $\sigma-\sigma^*$ and/or $n-\sigma^*$ transitions in $CHCl_3$, which leads to C−Cl bond cleavage.[23] The lamp (20 W, ø24 × 120 mm, illuminance: 2.00−2.33 and 5.96−8.09 mW/cm^2 at 185 and 254 nm, respectively) was inserted into the sample solution via a quartz glass jacket (ø28 × 150 mm) at the center of a cylindrical flask (ø42 × 170 mm) attached to a cooling condenser. Alternatively, when Cl_2, which was prepared upon mixing $Ca(ClO)_2$ with aqueous HCl, was added to the system (∼2%), a commercially available white LED (3 W, illuminance: 560 lux at 400−750 nm with a maximum intensity at λ = 465 nm) was attached to the outside of the flask. Scale-up synthesis could be done with larger flasks. Using the LPML, photochemical synthesis of NCA was demonstrated with an amino acid (2.5 mmol) suspended in a mixed solution of $CHCl_3$ and CH_3CN with or without an organic base under O_2 bubbling (0.1 L/min) with vigorous stirring at a variable temperature. The unreacted contents, such as $COCl_2$ and HCl, having high toxicity, generated by the reaction must be evacuated from the sample solution through incubation at >60 °C and removed by sequentially connecting two traps containing alcohol and alkaline water, respectively.

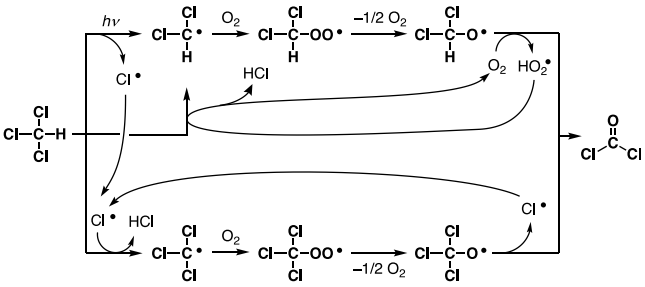
With the expectation that $COCl_2$ generated by the photochemical oxidation of $CHCl_3$ reacts with an amino acid, we initially examined in situ synthesis of NCA with L-phenylalanine (L-Phe) in $CHCl_3$. By reference to the standard conditions reported in our previous studies,[18b,20c] a 30 mL $CHCl_3$ solution containing 2.5 mmol of L-Phe was exposed to UV light under O_2 bubbling with stirring at 20 °C for 2 h (Table 1, entry 1A). However, only the HCl salt of L-Phe was obtained, without the formation of NCA. HCl generated by the oxidation of $CHCl_3$ may preferentially react with the amino acid to give the salt. When the reaction temperature was elevated to 60 °C, ^{1}H NMR analysis showed that the corresponding NCA was formed in 23% yield (entry 1B). In order to trap HCl generated in the reactions, which most likely decelerates the nucleophilic substitution of the amino acid to $COCl_2$, the reactions were carried out with organic bases with relatively high stability in the presence of light, such as pyridine and *N*-methylmorpholine (NMM). The yield of NCA was increased to 45% with pyridine (entry 1C). NMM, which is more basic than pyridine, increased the yield to 62% (entry 1D). However, the used organic bases underwent some photodecomposition,[24] and the resulting complex products contaminated the sample solution containing the produced NCA. This increases the time required for the post-purification process due to the increased amount of waste produced.

Thus, with a hypothesis that the observed low yield of NCA in entry 1B was due to the low solubility of the amino acid in $CHCl_3$, we examined a reaction with a mixture of $CHCl_3$ and CH_3CN. When the reaction was performed with a 1:1 (v/v) mixture of $CHCl_3$ and CH_3CN (2:3 molar ratio), the yield of NCA was increased to 48% (entry 1E). Upon elevating the reaction temperature to 70 °C, the product yield was further increased to >99% (entry 1F). The extraction of the product with CH_2Cl_2/water and subsequent recrystallization with diethyl ether/*n*-hexane allowed the isolation of L-Phe-NCA in a 89% yield. The observed decrease in the isolated yield is likely due to its decomposition by water (vide infra). Here, the generated HCl remaining in the sample solution further accelerated the acid-catalyzed decomposition of NCA.[8] Chiral HPLC analysis of the product in comparison with that of reference DL-Phe showed that no racemization occurred in this photochemical reaction (Figure S1). When the reaction was demonstrated under the same conditions using $CDCl_3$ instead of $CHCl_3$, NCA was also obtained in relatively lower 59% yield without deuteration (entry 1G). Further, quite interestingly, even with a 1:3 (v/v) mixture of $CHCl_3$ and CH_3CN (2:9 molar ratio), the photochemical reaction occurred to give NCA in 84% yield (entry 1H).

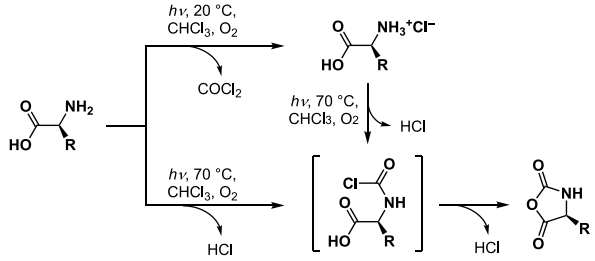
With respect to the reaction mechanism, CH_3CN decelerates the photochemical oxidation of $CHCl_3$ due to competitive absorption of UV-C light, but it may be inert to the generated Cl$^{\bullet}$, allowing the radical chain reaction to produce sufficient $COCl_2$ (Scheme 2a). $COCl_2$ reacts with L-Phe to give NCA via

Scheme 2. Proposed Mechanism for the Photochemical Reaction of Amino Acids with $CHCl_3$

(a) Photochemical Oxidation of $CHCl_3$



(b) Photochemical Formation of NCA



the formation of chlorocarbonyl-substituted L-Phe as an intermediate (Scheme 2b). In this mechanism, a minimum of 3 equiv amounts of HCl are theoretically generated when producing NCA, and some may react with L-Phe to give the corresponding HCl salt. However, it might also cause the reaction with $COCl_2$ at high temperature, similar to the cases for general syntheses of isocyanates with HCl salts of amines and $COCl_2$.[25] In support of this proposed mechanism, commercially available L-Phe·HCl was found to provide the corresponding NCA in 70% yield (Table 1, entry 1I). Thus, the reaction takes a longer time at higher temperature compared with other phosgenation reactions reported previously.[17−22] For safe handling of the reaction, the generated amount of $COCl_2$ should be regulated by ON−OFF cycles and/or intensity of the photo-irradiation, and the vaporized $COCl_2$ and generated HCl must be trapped with alcohol and alkaline water.

Similar photochemical reactions were demonstrated with L-leucine (L-Leu) and L-methionine (L-Met) (Table 1, entries 2 and 3) by varying the reaction conditions, and essentially the

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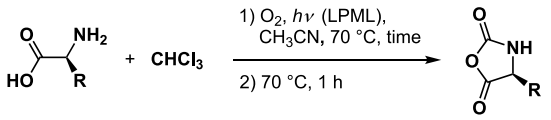
same trends were observed for this series of reactions. With the optimized conditions in entry 1F, these amino acids were converted to NCAs in 90 and 93% yields, respectively, in the solution (entries 2E and 3D, respectively). The relatively lower yields observed compared to those for L-Phe may be due to their lower solubilities. Although Met is known to undergo oxidation on its thioether group,[26] no notable side reaction was observed. These NCAs produced were then isolated in 85 and 52% yields, respectively, with the same procedures in the case of L-Phe-NCA. The notable decrease in the yield of L-Met is probably due to its higher solubility in water, which accelerates its decomposition (vide infra).

Scale-up syntheses of NCAs were then demonstrated with L-Phe and L-Leu (Table 2). For these experiments, the

Table 2. Scale-Up Syntheses of Amino Acid NCAs



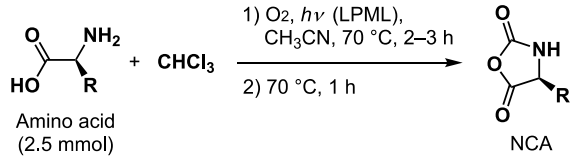
entry	amino acid	$CHCl_3$ (mL)	solvent (mL)	time (h)[a]	NCA yield (%)[b]
1	L-Phe 55 mmol (9.1 g)	80	80	2.25	87
2	L-Leu 30 mmol (3.9 g)	80	80	2.75	67

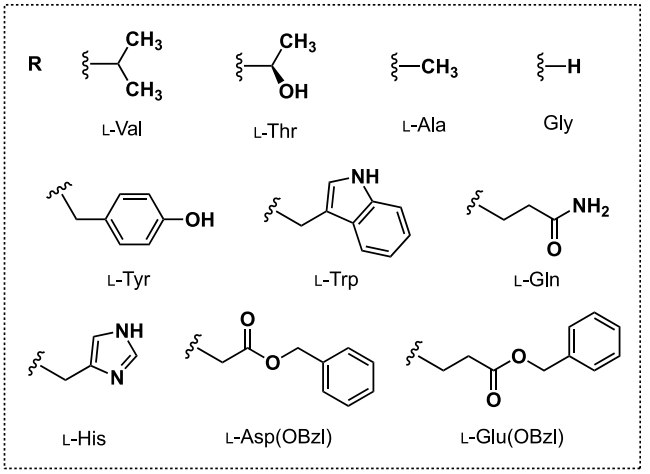
[a]Repeated 5 min ON and 10 min OFF of photo-irradiation with LPML. [b]Isolated yield.

cylindrical flask was changed to a conventional larger three-neck round-bottom flask (1.0 L). The photochemical reactions were conducted with a mixed solution of $CHCl_3$ (80 mL, 1.0 mol) and CH_3CN (80 mL, 1.5 mol) containing 9.1 g (55 mmol) of L-Phe or 3.9 g (30 mmol) of L-Leu, and the corresponding NCAs were obtained in 87 and 67% yields, respectively, after the purifications.

With the above optimized conditions, we have further demonstrated photochemical synthesis of NCAs with a series of α-amino acids (Table 3). L-Valine (L-Val), having a shorter branched alkyl group than L-Leu, showed the photochemical conversion to NCA in 93% yield, and it could be isolated in 82% yield (entry 1). The observed decrease in the isolated yield may also be attributed to the decomposition of NCA in the extraction. As a support of this proposed decomposition-mechanism, L-Val-NCA dissolved in water underwent hydrolysis upon sonication (38 kHz, 300 W) at 40 °C for 15 min to reproduce the corresponding α-amino acid in 38% yield. L-Threonine (L-Thr), having an aliphatic OH group on the alkyl group, showed lower 28% conversion, but the corresponding NCA could not be isolated (entry 2).[8] The attached OH group may decelerate photochemical oxidation of $CHCl_3$ to decrease the conversion and further the increase solubility of NCA into water to accelerate its decomposition. L-Alanine (L-Ala) with methyl group, and glycine (Gly) without the substituent group, both with lower solubilities into $CHCl_3/CH_3CN$, produced NCAs in 59 and 31%, respectively (entries 3 and 4, respectively). The observed larger decrease in the isolated yields of Gly-NCA may also be ascribed to its relatively higher solubility in water. L-Tyrosine (L-Tyr), bearing an aromatic OH group, also brought about the reaction, but showed a clear decrease in yield to 50% compared with L-Phe (entry 5). This is likely due to its lower solubility in organic solvents and the attached OH group that inhibits the photochemical oxidation

Table 3. Photochemical Syntheses of Amino Acid NCAs with UV Light under Optimized Reaction Conditions[a]





entry	amino acid	yield (%) ^{1}H NMR	yield (%) isolated	ee (%)[b]
1	L-Val	93	82	>99
2	L-Thr	28		
3	L-Ala	67	59	>99
4	Gly	56	31	
5	L-Tyr	56	50	>98
6	L-Trp	44	40	>99
7	L-Gln			
8	L-His			
9	L-Asp(OBzl)	90	89	>98
10	L-Glu(OBzl)	92	91	>98

[a]Reaction conditions: photo-irradiation repeated 5 min ON and 10 min OFF with LPML. [b]Enantiomeric excess determined by chiral HPLC analysis.

of $CHCl_3$. Here, no notable side-products, which were expected from the reactions of the unprotected phenolic OH group, were observed, probably due to their lower nucleophilicity than the aliphatic OH groups. L-Tryptophane (L-Trp), whose lone pair on the NH group is incorporated in the aromatic π-conjugation system, provided NCA in 40% yield (entry 6). However, L-glutamine (L-Gln), which is insoluble in $CHCl_3/CH_3CN$ solvent, and L-histidine (L-His), which includes a basic imidazole group capable of binding HCl, showed no conversions to NCAs (entries 7 and 8, respectively). Benzyl-protected α-amino acids such as 4-benzyl L-aspartate [L-Asp(OBzl)] and 5-benzyl L-glutamate [L-Glu-(OBzl)] provided the corresponding NCAs in higher yields of 89% and 91% , respectively (entries 9 and 10, respectively). These results suggest that NCA can be obtained in higher yield with the substituent group having the following properties: (1) inactive for the photochemical oxidation of $CHCl_3$, (2) inert to HCl, and (3) high lipophilicity.

The reaction was further available to secondary amino acids. Sarcosine (Sar), having *N*−methyl group, provided the corresponding NCA in 62% yield [Scheme 3, reaction (a)]. *tert*-Butoxycarbonyl (Boc) protected L-Asp(OBzl) [Boc-L-

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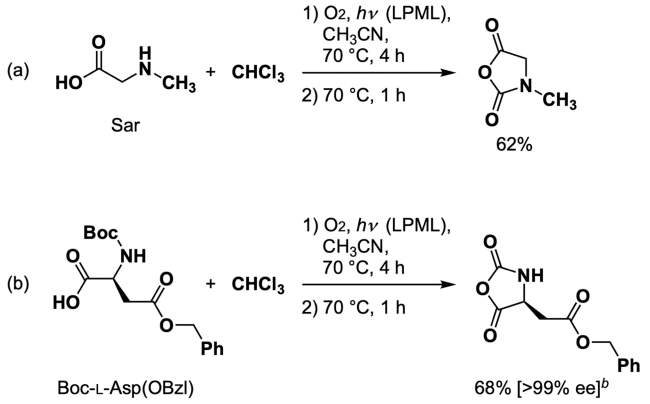
Scheme 3. Photochemical Syntheses of Amino Acid NCAs from N-Substituted Amino Acids with UV Light[a]

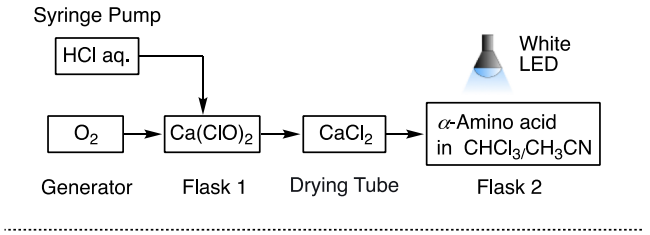


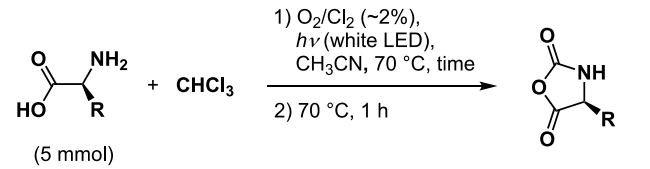
[a]Repeated 5 min ON and 10 min OFF of photo-irradiation with LPML. [b]Enantiomeric excess determined by chiral HPLC analysis.

Asp(OBzl)] provided L-Asp(OBzl)-NCA in 68% yield with deblocking of Boc group [reaction (b)]. The deblocking occurred in these reactions is most likely due to HCl generated by the photochemical oxidation of $CHCl_3$ and by the reaction of amino acid with $COCl_2$.[27]

With recent global concerns about the use of mercury lamps, which should be avoided due to their large environmental impacts and health hazards,[28] we further demonstrated the photochemical synthesis of NCA with visible light upon mixing a small amount of Cl_2 (~2%) with O_2 gas. Although the reaction time was increased, a 1:1 (v/v) mixture of $CHCl_3$ and CH_3CN containing L-Phe or L-Leu provided the corresponding NCAs in 65% and 60% yields, respectively, without notable side products (Table 4). As a control, without Cl_2, L-Phe showed no reaction. In terms of the reaction mechanism, Cl_2 may undergo homolytic cleavage to give 2 $Cl^{\bullet}$ upon exposure to visible light and initiate the radical chain reaction to produce

Table 4. Syntheses of Amino Acid NCAs with Visible Light[a]





entry	amino acid	$CHCl_3$	CH_3CN	time (h)	NCA yield (%)[b]
1	L-Phe	15	15	8	65 [>99% ee][c]
2	L-Leu	15	15	8	60 [>99% ee][c]

[a]Schematic diagram of the reaction system and results of the reactions. Irradiation with visible light from a 3 W white LED lamp of a suspended $CHCl_3$ solution (15 mL) containing 5 mmol of α-amino acid under bubbling with O_2 (0.1 L·min^{-1}) and ~2% Cl_2. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC analysis.

$COCl_2$ from $CHCl_3$. The observed decrease in yields of NCAs compared with the results of 1F and 2E in Table 1 may be ascribed to the lower efficiency of the photochemical conversion of $CHCl_3$ to $COCl_2$ in this system.

CONCLUSIONS

In this study, we found that photochemical oxidation of $CHCl_3$ occurred with a polar CH_3CN solvent. We successfully applied this reaction to the synthesis of a variety of NCAs from α-amino acids having hydrophilic structures. Compared with the reactions with BTC and other phosgene substitutes, the present reaction has clear advantages in terms of simplicity, cost, and environmental impact. Furthermore, compared with conventional reactions directly using $COCl_2$, this reaction is safer and more convenient under controlled light without the need for a special apparatus or reagents, while maintaining the advantages of $COCl_2$. However, the present reaction still has the potential disadvantage of generating HCl, which accelerates the decomposition of the produced NCAs. Overall, this reaction is expected to be an innovative practical method for synthesizing NCAs in both academia and industry.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Oxygen gas (concentration: 90%) was produced from air with an oxygen generator (GL Science Inc. OM-904C). All ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer, where chemical shifts (δ in ppm) were determined with respect to tetramethyl silane (TMS) as an internal standard. Chiral HPLC was performed at 20 °C on a JASCO LC-2000 HPLC system with DAICEL CHIRALPAK IC-3 columns using a JASCO Type PU-2089 quaternary gradient pump and equipped with a JASCO MD-2018 Plus photodiode array detector and a JASCO Type RI-4030 refractive index detector with *n*-hexane/THF (4:1 or 3:2) as an eluent at the flow rate of 0.5 mL/min.

General Procedure for the Photochemical Synthesis of NCAs with a LPML. A cylindrical flask (ø42 × 120 mm), equipped with an LPML (Sen Light Co., UVL20PH-6, 20 W, ø24 × 120 mm), a cooling condenser (0 °C), and a magnetic stirring bar, was charged with a mixture solution of $CHCl_3$ (15 mL) and CH_3CN (15 mL) containing an α-amino acid (2.5 mmol). An aluminum block bath was used to heat the sample solution. The sample solution was vigorously stirred upon bubbling with O_2 (0.1 L/min) under exposure to the UV light by repeating 5 min ON and 10 min OFF for 2 or 3 h at 70 °C. The lamp was turned off, and the sample solution was stirred at 70 °C for 1 h to remove the unreacted $COCl_2$ and generated HCl dissolved in the solution. The yield of the product was determined by ^1H NMR analysis with CH_2Cl_2 or $C_2H_2Cl_4$ as an internal standard. For the isolation of the product, the resulting sample solution was then washed with water and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was recrystallized with THF, diethyl ether, or CH_2Cl_2 and *n*-hexane to give the corresponding NCA. All products were unambiguously characterized by means of ^1H and ^{13}C NMR spectroscopy in reference to the previous reports.[8,9b,15]

General Procedure for the Photochemical Synthesis of NCAs with a White LED. $Ca(ClO)_2$ (2.14 g, 15 mmol) was charged to a three-neck round-bottom flask (flask 1),

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equipped with a syringe pump. Flask 1 was further connected to a 100 mL of three-neck round-bottom flask (flask 2) via a calcium chloride tube. The flask 2 was charged with a mixture solution of $CHCl_3$ (15 mL) and CH_3CN (15 mL) containing an α-amino acid (2.5 mmol). Under steady flow of O_2 (0.1 L/min), 20 mL of an aqueous HCl solution (6 M) was continuously added to flask 1 by the syringe pump at room temperature for 8 h. A water bath was used to heat up the sample solution. The sample was stirred at 70 °C for 8 h under bubbling with the prepared O_2/Cl_2 gas and photo-irradiation with a 9 W white LED. The lamp was turned off, and the sample solution was stirred at 70 °C for 1 h to remove the unreacted $COCl_2$ and generated HCl dissolved in the solution. The resulting sample solution was then washed with water and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was recrystallized with THF and *n*-hexane to give the corresponding NCA. All products were unambiguously characterized by means of ^1H and ^{13}C NMR spectroscopy.

Characterizations of the Isolated NCAs. *(S)-4-Benzyloxazolidine-2,5-dione [L-Phe-NCA].* White solid; yield: 0.43 g, 89%; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ/ppm 7.40−7.31 (m, 3H, Ph), 7.21−7.19 (m, 2H, Ph), 5.61 (br s, 1H, NH), 4.53 (dd, J = 8.8, 4.0 Hz, 1H, NHC<u>H</u>), 3.32 (dd, J = 14.0, 4.0 Hz, 1H, CH_2), and 2.98 (dd, J = 14.0, 8.8 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ/ppm 168.6, 151.5, 133.9, 129.3, 129.1, 128.1, 58.8, and 37.9.

(S)-4-Isobutyloxazolidine-2,5-dione [L-Leu-NCA]. White solid; yield: 0.33 g, 85%; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ/ppm 6.16 (br s, 1H, NH), 4.34 (dd, J = 9.2, 4.4 Hz, 1H, NHC<u>H</u>), 1.88−1.78 (m, 2H, CH_2), 1.72−1.67 (m, 1H, CH), 1.01 (d, J = 6.4 Hz, 3H, CH_3), and 0.99 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ/ppm 169.7, 152.2, 56.1, 40.8, 25.1, 22.7, and 21.6.

(S)-4-(2-(Methylthio)ethyl)oxazolidine-2,5-dione [L-Met-NCA]. White solid; yield: 0.23 g, 52%; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ/ppm 6.52 (s, 1H, NH), 4.49 (dd, J = 7.8, 4.2 Hz, 1H, CH_2), 2.74−2.68 (m, 2H, CH_2), 2.36−2.26 (m, 1H, CH_2), 2.12 (s, 3H, CH_3), and 2.10 (sext, J = 8.0 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ/ppm 170.1, 152.8, 56.5, 30.1, 29.5, and 15.0.

(S)-4-Isopropyloxazolidine-2,5-dione [L-Val-NCA]. White solid; yield: 0.29 g, 82%; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ/ppm 5.98 (br, 1H, NH), 4.22 (dd, J = 4.4, 4.0 Hz, 1H, CH), 2.26 (dtt, J = 6.8, 6.8, 4.0 Hz, 1H, CH), 1.09 (d, J = 6.8 Hz, 3H, CH_3), and 1.04 (d, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ/ppm 168.8, 153.3, 63.1, 30.8, 18.3, and 16.6.

(S)-4-Methyloxazolidine-2,5-dione [L-Ala-NCA]. White solid; yield: 0.17 g, 59%; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ/ppm 6.24 (br s, 1H, NH), 4.42 (q, J = 6.4 Hz, 1H), and 1.58 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ/ppm 170.3, 152.6, 53.4, and 17.6.

Oxazolidine-2,5-dione [Gly-NCA]. White solid; yield: 0.08 g, 31%; ^1H NMR (400 MHz, DMSO-d_6, 293 K): δ/ppm 8.84 (br s, NH, 1H) and 4.19 (s, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ/ppm 169.9, 153.5, and 46.7.

(S)-4-(4-Hydroxybenzyl)oxazolidine-2,5-dione [L-Tyr-NCA]. White solid; yield: 0.26 g, 50%; ^1H NMR (400 MHz, DMSO-d_6, 293 K): δ/ppm 9.35 (s, 1H, OH), 9.04 (s, 1H, NH), 6.96 (d, J = 8.4 Hz, 2H, Ph), 6.68 (d, J = 8.4 Hz, 2H, Ph), 4.70 (t, J = 5.0 Hz, 1H, CH_2), and 2.90 (dd, J = 4.8, 2.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ/ppm 171.4, 156.9, 152.2, 131.2, 125.0, 115.6, 59.0, and 35.9.

(S)-4-((3-Indolyl)methyl)oxazolidine-2,5-dione [L-Trp-NCA]. White solid; yield: 0.23 g, 40%; ^1H NMR (400 MHz, DMSO-d_6, 293 K): δ/ppm 11.00 (br s, 1H), 9.08 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.07 (dt, J = 8.0, 0.8 Hz, 1H), 6.99 (dt, J = 8.0, 0.8 Hz, 1H), 4.78 (t, J = 5.2 Hz, 1H), 3.22 (dd, J = 15.0, 5.0 Hz, 1H), and 3.16 (dd, J = 15.0, 5.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ/ppm 171.3, 151.9, 136.0, 127.2, 124.5, 121.1, 118.6, 118.5, 111.5, 107.1, 58.3, and 26.5.

Benzyl (S)-3-(2,5-Dioxooxazolidin-4-yl)propanoate [L-Asp(OBzl)-NCA]. White solid; yield: 0.56 g, 89%; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ/ppm 7.41−7.34 (m, 5H), 6.35 (s, 1H), 5.19 (s, 2H), 4.59 (dd, J = 9.2, 2.4 Hz, 1H), 3.09 (dd, J = 8.8, 3.2 Hz, 1H), and 2.85 (dd, J = 18.0, 9.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ/ppm 169.4, 168.5, 151.8, 134.6, 128.8, 128.7, 128.5, 67.8, 53.9, and 35.9.

Benzyl (S)-3-(2,5-dioxooxazolidin-4-yl)butanoate [L-Glu-(OBzl)-NCA]. White solid; yield 0.60 g, 91%; ^1H NMR (400 MHz, DMSO-d_6, 293 K): δ/ppm 9.11 (s, 1H), 7.41−7.30 (m, 5H), 5.10 (s, 2H), 4.49−4.45 (m, 1H), 2.54−2.48 (m, 2H), 2.10−2.00 (m, 1H), and 1.99−1.89 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ/ppm 172.0, 171.5, 152.1, 136.2, 128.7, 128.3, 128.2, 66.0, 56.5, 29.3, and 26.7.

3-Methyloxazolidine-2,5-dione [Sar-NCA]. White solid; yield: 0.18 g, 62%; ^1H NMR (400 MHz, DMSO-d_6, 293 K): δ/ppm 4.22 (s, 2H, CH_2) and 2.86 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ/ppm 167.9, 153.0, 51.6, and 30.3

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05299.

Chiral HPLC profiles of NCAs, experimental procedures, and copies of ^1H and ^{13}C NMR spectra (PDF)

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