N-Carboxyanhydrides Directly from Amino Acids and Carbon Dioxide and their Tandem Reactions to Therapeutic Alkaloids

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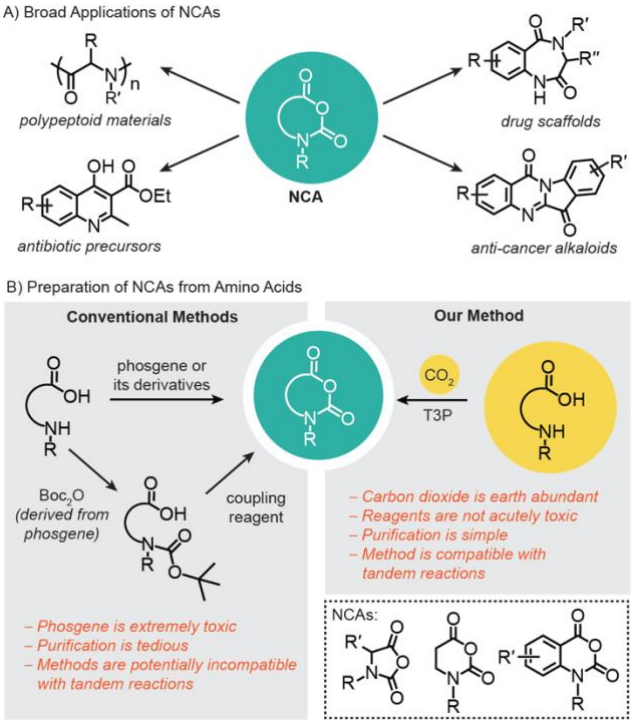
We report on the preparation of synthetically versatile *N*-carboxyanhydrides (NCAs) directly from amino acids and CO_2 using *n*-propylphosphonic anhydride. Most of the NCAs were isolated with >95% purity after simple workup, avoiding the need for tedious purification procedures typically required using conventional methods. Because the reagents and conditions employed are mild, tandem reactions with moisture-sensitive NCAs were carried out to transform them into the medicinally active alkaloids tryptanthrin and phaitanthrin A in one pot. A qualitative analysis revealed that our NCA synthesis approach is more green than conventional methods, which all directly or indirectly use the highly poisonous gas phosgene.

Introduction

The use of abundant feedstocks offers the possibility of creating a renewable carbon economy.[1-3] CO_2 is a versatile C1 building block in synthesis due to its availability, nontoxicity, and recyclability. An area that could achieve greater sustainability from the direct use of CO_2 is the formation of *N*-carboxyanhydrides (NCAs),[4] which are cyclic amino acid derivatives used widely in the synthesis of designer molecules and polymers (Scheme 1A). Five-membered ring NCAs are valuable monomers in the synthesis of polyamides[5-8] for surface coatings,[9, 10] drug delivery,[11, 12] or peptide-based drugs.[13, 14] Six-membered ring NCAs are important synthons in the preparation of alkaloids with potent anti-tumor, anti-malarial, and anti-parasitic activity.[15-18] For example, about 30-40% of six-membered ring NCA isatoic anhydrides made globally are used for the production of pharmaceuticals and chemical intermediates.[19]

Although several methods have been reported for the preparation of NCAs from amino acids, they suffer from high toxicity or reactive side products that are difficult to remove (Scheme 1B). NCAs are most commonly synthesized using the Fuchs-Farthing reaction between amino acids and the extremely poisonous gas phosgene, or the treatment of *N*-alkyloxycarbonylamino acids with coupling reagents.[20-22] Precursors based on *N*-alkyloxycarbonylamino acids are obtained using di-*tert*-butyl dicarbonate (Boc_2O), which unfortunately is made from phosgene ($COCl_2$). Safer coupling reagents, such as triphosgene and carbonate esters, either produce $COCl_2$ in situ or are also derived from $COCl_2$, respectively.[23] Thus, these activators are unfavorable due to their possible negative impacts on human health and the environment. Other strategies to obtain NCAs from non-amino acid starting materials can only furnish 6-membered ring NCAs and/or the precursors require multistep synthesis from commercial starting materials.[24-28]



Scheme 1. A) Examples of the many applications of NCAs in the production of designer molecules and polymers. B) Comparison of methods for the synthesis of *N*-carboxyanhydrides (NCAs) from amino acids. In conventional NCA synthesis, phosgene or coupling reagents obtained from phosgene (e.g., carbonate esters), or derivatives that generate phosgene in situ (e.g., triphosgene) are used.

We are interested in developing safe, sustainable, and simple NCA synthetic approaches mild enough to be used in tandem reactions. Thus, we propose a new method to access five- and six-membered rings directly from amino acids and the

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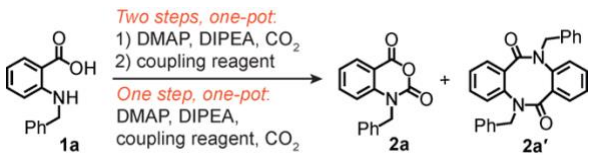
earth abundant C1 source carbon dioxide.[29-34] Our strategy is to combine three chemical processes in one-pot: 1) formation of carbamate from amine and CO_2; 2) activation of carboxylic acid; and 3) ring-closing to form C-O bonds. Herein, we demonstrate for the first time the coupling of these elementary steps to form NCAs with high efficiency. We found that the nature of the coupling reagent is key to obtaining exclusive selectivity for NCAs over amino acid dimers.[35] Our NCA synthesis approach has a broad substrate scope and can be used in tandem reactions to produce bioactive alkaloids. Because our method employs CO_2, does not use toxic reagents, and generates products with high purity in most cases, it is more favorable than conventional methods based on several green chemistry metrics (Scheme 1B).

Results and Discussion

Because amino acids are bifunctional, we needed to identify coupling reagents that could selectively activate the carboxylic acid without reacting with the amine. Among the numerous amide coupling reagents known,[36] we favored *n*-propylphosphonic anhydride (T3P) because it has low toxicity, long shelf life, easy handling, and byproducts that are water soluble so they can be washed away during workup.[37] In addition, T3P can serve as a water scavenger to enable isolation of moisture sensitive five-membered ring NCAs.

Table 1. Comparing Two-Step vs. One-Step Reactions[a]

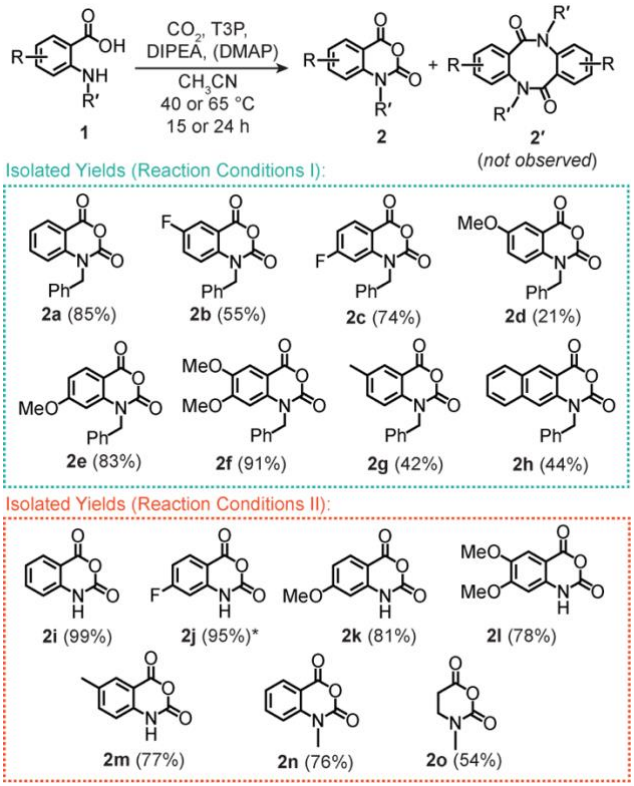


Entry	Method	Coupling Reagent (equiv.)	Yield (%)	2a:2a'
1	two-steps	T3P (1.5)	80	100:8
2	two-steps	T3P (3.0)	82	100:1
3	two-steps	CMPI (1.5)	54	100:20
4	two-steps	CDI (1.5)	0	-
5	two-steps	DPC (1.5)	0	-
6	two-steps	DPA (1.5)	0	-
7	one-step	T3P (1.5)	56	100:1
8	one-step	T3P (3.0)	85	100:0

[a]Two-step method: Combined **1a** (1.0 eqiuv.), DMAP (1.0 equiv.), DIPEA (4 equiv.) under CO_2 (300 psi) in 50 mL of MeCN at 65°C for 2 h. Added T3P (varied) and stirred for 24 h at 65 °C. One-step method: combined all reagents at the same time, pressurized with CO_2, and stirred at 65 °C for 24 h. See Tables S3 and S4 for more details. T3P = *n*-propylphosphonic anhydride, CMPI = 2-chloro-1-methylpyridinium iodide, CDI = *N,N*-carbonyldiimidazole, DPC = diphenylphosphinic chloride, DPA = diphenylphosphinic acid.

Initially, we tested a one-pot, two-step procedure by treating 2-(*N*-benzylamino)benzoic acid (**1a**, Table 1) or 2-aminobenzoic acid (**1i**, Table S2) with 4-dimethylaminopyridine (DMAP) and di-*iso*-propylethylamine (DIPEA) under CO_2 to form the corresponding carbamate, followed by the addition of a coupling reagent to promote ring closing. DMAP was used as a co-activator due to its ability to generate electrophilic acylpyridinium species.[38, 39] When 1.5 equivalents of T3P relative to **1a** was employed, 80% yield of NCA **2a** was obtained along with 6% of dimer **2a'** after an ethyl acetate-water workup (Table 1, entry 1). Increasing the quantity of T3P to 3.0 equivalents afforded 82% product yield but significantly reduced dimer yield (0.8%, entry 2). Reactions employing other phosphorus-based reagents such as diphenylphosphinic chloride (DPC, entry 5) or diphenylphosphinic acid (DPA, entry 6) showed full starting material conversion but no NCA products. Poor selectivity for **2a** over **2a'** was achieved using 2-chloro-1-methylpyridinium iodide (CMPI) (entry 3) and *N,N*-carbonyldiimidazole (CDI) was completely ineffective (entry 4). To optimize the T3P reaction, we found that when all starting materials were combined at the same time in a one step on-pot procedure, **2a** was isolated in 85% yield with no dimers (entry 8).

Table 2. Synthesis of Six-Membered Ring NCAs[a]



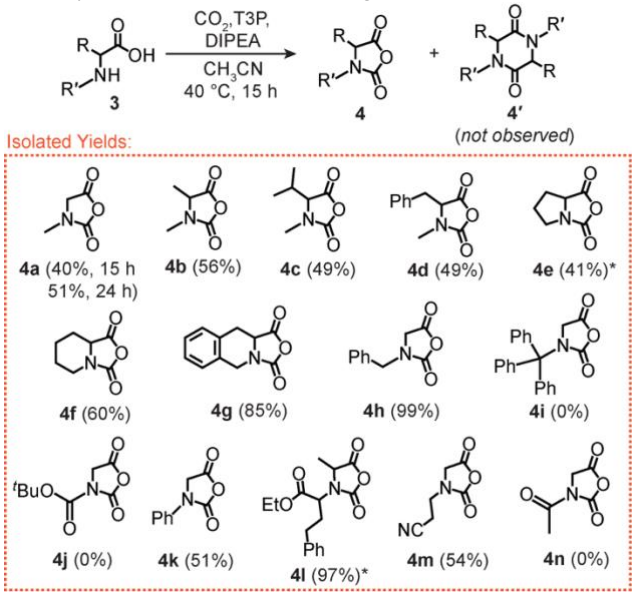
[a]Compounds **2a**-**2h** were synthesized using reaction conditions I (Method E in the SI): **1** (1.0 equiv.), CO_2 (300 psi), T3P (3.0 equiv.), DIPEA (4.0 equiv.), and DMAP (1.0 equiv.) in 40 mL of CH_3CN at 65 °C for 24 h. Compounds **2i**-**2o** were synthesized using reaction conditions II (Method F in the SI): **1** (1.0 equiv.), CO_2 (300 psi), T3P (3.0 equiv.), and DIPEA (4.0 equiv.) in 40 mL of CH_3CN at 40 °C for 15 h.

Using our optimized conditions (I, Table 2), we screened a variety of 2-(*N*-benzylamino)benzoic acid derivatives to form six-membered ring NCAs. Substrates fluorinated at the 5-position (**1b**) and the 4-position (**1c**) of the benzoic acid ring were converted to **2b** (55%) and **2c** (74%) in moderate yields, respectively. Although **1d** featuring a 5-methoxy substituent gave a low yield of **2d** (21%), **1e** featuring a 4-methoxy substituent gave a high yield of **2e** (83%). When the substrate was functionalized with 4,5-dimethoxy (**1f**), the corresponding **2f** was isolated in 91% yield. We propose that in **2d**, the 5-methoxy group can withdraw electrons inductively so it makes the NCA more reactive toward water used in the workup step, resulting in its low isolated yield. In contrast, **2e** and **2f** contain 4-

methoxy substituents that donates electrons to the C=O group *para* to it, reducing the electrophilicity of the NCA. Finally, 5-methylated **1g** and benzo-fused **1h** were transformed to NCAs with moderate efficiency (42% for **2g** and 44% for **2h**). The majority of NCAs were isolated with >95% purity using a simple organic-aqueous workup procedure. Circumventing the need for further purification by recrystallization, sublimation, or column chromatography is a significant advantage of our NCA synthesis method over conventional methods.[20]

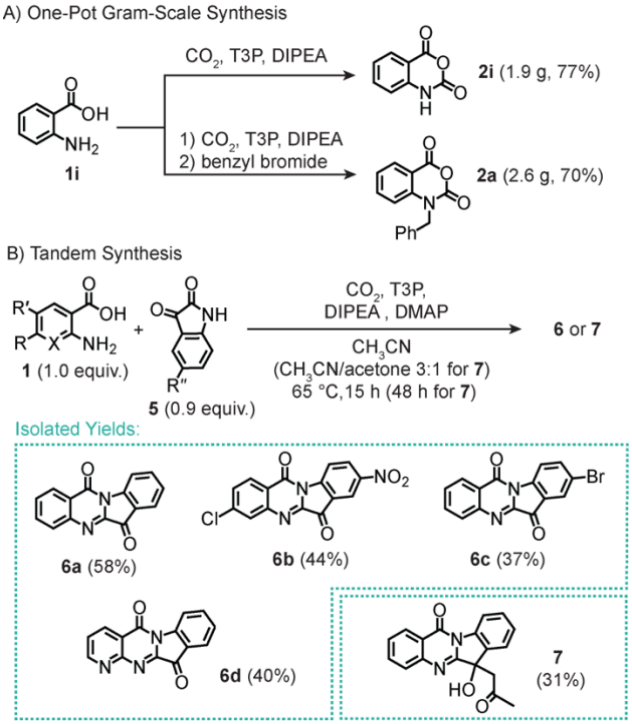
Because *N*-unsubstituted NCAs are considerably more reactive than *N*-benzylated NCAs, it was necessary to modify our reaction conditions to maximize their isolated yields (II, Table 2). We found that the presence of DMAP (Figure S16) and elevated temperatures led to the degradation or polymerization of *N*-unsubstituted NCAs. Thus, we altered our standard conditions to exclude DMAP, decreased the temperature to 40 °C, and shortened the reaction time to 15 h. This modified protocol afforded *N*-unsubstituted NCAs with excellent yields. For example, the parent substrate **1i** was converted to **2i** in >99% yield, whereas substrates containing methoxy or methyl substituents (**2k**-**2m**) were converted to their corresponding NCAs in ~80% isolated yields. Compound **2j** could be isolated in 95% yield, despite being prone to degradation upon prolonged exposure to moisture. Lastly, 2-(*N*-methylamino)benzoic acid (**1n**) and 3-(*N*-methylamino)propanoic acid (**1o**) were transformed to **2n** and **2o** in 76 and 54% yield, respectively. The latter indicates that aliphatic six-membered ring NCAs can also be synthesized using our approach. For comparison, a Pd-based method used to obtain isatoic anhydride was unable to produce aliphatic NCAs because it requires weak carbon(sp^2)–iodide bonds for oxidative addition to occur.[26]

Table 3. Synthesis of Five-Membered Ring NCAs[a]



[a]Reaction conditions used (Method F in the SI): **3** (1.0 equiv.), CO_2 (300 psi), T3P (3.0 equiv.), and DIPEA (4.0 equiv.) in 40 mL of CH_3CN at 40 °C for 15 h. The *L*-enantiopure starting material was used for **4c**-**4e** and **4l** whereas the *D*,*L*-racemates were used for **4b** and **4f**. NCAs **4e** and **4l** were synthesized at 30 °C for 36 h.

Our modified method using reaction conditions II was also effective for the preparation of five-membered ring NCAs from α-amino acids (Table 3). We observed that *N*-methylated glycine (**3a**), alanine (**3b**), valine (**3c**), and phenylalanine (**3d**) were transformed into their corresponding NCAs in 40-56% isolated yields. Proline (**3e**) and other cyclic compounds **3f** and **3g** were successfully converted to **4e**, **4f**, and **4g**, respectively, in moderate to high yields (41-85%). Because polyproline materials have many useful applications,[40] NCAs derived from **1e** are in high demand. Once again, we were able to obtain NCA products with high purity after workup, which makes our approach more efficient than those requiring complicated procedures to remove unreacted starting materials and uncyclized acyl chloride impurities.[20, 41] Reactions using various *N*-substituted glycine starting materials revealed that those bearing benzyl (**3h**), phenyl (**3k**), and cyanoalkyl (**3m**) groups were well tolerated. However, substrates featuring bulky (**3i**) or electron-withdrawing (**3j**, **3n**) *N*-substituents could not be converted to NCAs because their nitrogen donors are either too sterically hindered or deactivated to react. The alanine derivative **3l**, which is a precursor to an angiotensin-converting enzyme inhibitor medication,[42] was converted to **4l** with high efficiency (97% yield). Because of their reactive nature, **4e** and **4l** were synthesized at 30 °C for 36 h. We found that subjecting *N*-unsubstituted α-amino acids to our standard conditions gave polymers, which is likely due to polymerization of the in situ generated NCAs.[43]



Scheme 2. Synthesis of alkaloids **6** and **7** using stepwise (A) and tandem (B) reactions. Experimental procedures are given in the SI.

For practical applications, our method could be used to synthesize NCAs on a gram scale. For example, starting from **1i**, 1.9 g of **2i** (77% yield) was obtained in analytically pure form without the need for column chromatography or recrystallization (Scheme 2A). We found that *N*-benzylated **2a** could be prepared from **1i** using a one-pot two step procedure. When **1i** was treated with T3P and DIPEA under CO_2, followed by treatment with benzyl bromide, **2a** was isolated in 2.6 g (70% yield) with excellent purity. We anticipate

that this approach will enable rapid preparation of a large library of *N*-alkylated NCAs.

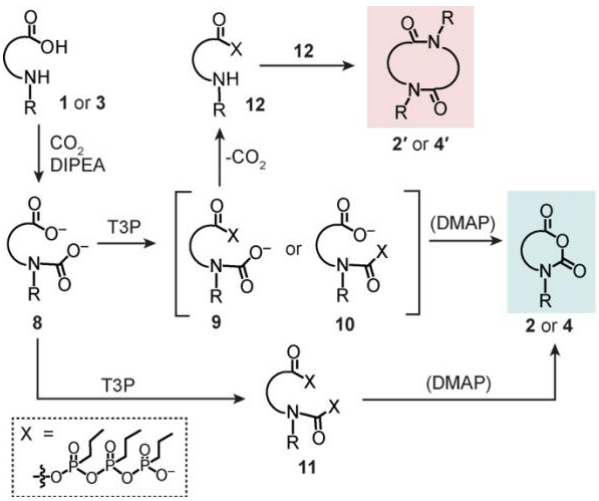
Next, we focused on developing one-pot multi-step processes to construct therapeutic alkaloids starting from amino acids and CO_2. Tryptanthrin (**6a**) and its derivatives were selected as synthetic targets because they have well-documented medicinal properties.[15, 44-46] In conventional synthesis, tryptanthrin can be prepared in two steps by converting **1i** to **2i**, followed by reaction with isatin (**5a**, Scheme S1). Aldol addition between tryptanthrin and acetone provides phaitanthrin A (**7**), which is a natural product with promising anti-cancer activity.[47, 48] In our tandem reaction studies, we combined **1i**, **5a**, T3P, DIPEA, and DMAP under 300 psi of CO_2. The desired product **6a** was isolated in 58% yield as a yellow solid after purification. Time dependence studies suggest that the conversion of **1i** to **6a** proceeds via the NCA intermediate **2i** (Figure S10).

Using our optimized reaction conditions, several tryptanthrin derivatives were prepared (Scheme 2B). Compounds **6b**, **6c**, and **6d** were isolated in 44, 37, and 40% yield, respectively. When **1i**, **5a**, T3P, DIPEA, and DMAP were combined in a mixture of CH_3CN/acetone (3:1) under CO_2 (Table S7), the alkaloid **7** was identified as the primary product with only trace amounts of **6a**. Although the linear synthesis of **7** starting from 2-aminobenzoic acid has not yet been reported, we estimated the overall yield for the sequence **1i**→**2i**→**6a**→**7** (Scheme S1) to be ~60% based on the expected yields of the individual steps (89,[49] 90,[17] and 77%[50], respectively). Our isolated yield of 31% for **7** is moderate but because it was obtained from a one-pot tandem reaction, there are reductions in cost, time, labor, and waste compared to that of products obtained from the three-step reactions in Scheme S1. Additionally, coupling NCA synthesis with subsequent reactions allows us to take advantage of intermediates that would otherwise be unstable under certain conditions. For example, when **1i** was subjected to our standard conditions in the presence of DMAP, only 11% of **2i** was isolated (Table S2, entry 10). However, the addition of **5a** as both a "trap" and coupling partner with the reactive **2i**, led to the isolation of **6a** in 58% yield (Scheme 2B).

Experiments were performed to determine the carbonyl source in the newly synthesized NCAs (Scheme S2). When **1a** was exposed to $^{13}CO_2$ (15 psi) using our standard NCA synthesis conditions, the product isolated had an *m*/*z* value of 254.4 (Figures S6), consistent with the molecular mass expected for a ^{13}C-labeled NCA (^{13}C-**2a**). No isotope enrichment was observed in the dimer product **2a'**. Characterization of ^{13}C-**2a** by ^{13}C NMR spectroscopy showed a prominent signal at 148.6 ppm (Figure S1), which was significantly more intense than that in the parent **2a** sample. These measurements confirm that the C=O adjacent to nitrogen in the NCA structure is derived from CO_2.

To gain insight into the reaction mechanism, we carried out a series of control studies using **1a** as a model substrate. When T3P was omitted, neither NCA nor amino acid dimer products had formed (Table S8, entry 4). The NCA yields decreased sharply when DIPEA (2.5%, entry 2) or DMAP (10%, entry 3) were excluded. Because omitting DIPEA gave lower yields than omitting DMAP, this result suggests that having a bulky base to promote carbamate formation is critical to efficient NCA synthesis. Reactions performed using other strong amine bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_3CN/DMSO (1:1) also furnished **2a** in good yield (58%) under much lower CO_2 pressure (15 instead of 300 psi) (Table S9). However, DBU can initiate polymerization of five-membered ring NCAs so it was not explored further in this work.[51] Our solvent studies revealed that CH_3CN provided NCAs with the highest yield (Table S5), presumably due to its greater polarity and better CO_2 solubility in comparison to other common organic solvents (e.g., THF, carbonate ester, and propylene oxide).[52] Gas pressure studies showed that dimer formation was fully suppressed when CO_2 was maintained at ≥150 psi (Table S4). Our experimental (Scheme S4) and computational results (Scheme S3) confirmed that both carboxylic acid and carbamate moieties in amino acids could be activated by T3P.

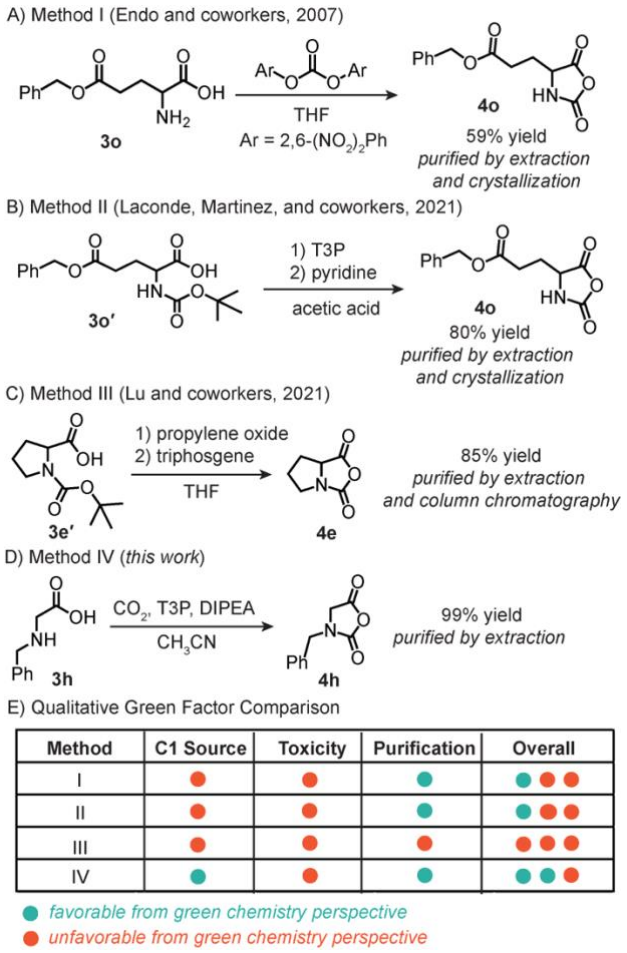
On the basis of these results, a possible mechanism is proposed in Scheme 3. Starting from amino acid **1** or **3**, DIPEA deprotonates the N-H and O-H groups to form a dianion that reacts with CO_2 to give **8**. The carboxylate or carbamate in **8** could attack T3P to generate the activated intermediates **9** or **10**, respectively. These species then undergo ring closing to furnish the desired NCAs. However, when the CO_2 pressure is below 150 psi, **9** decarboxylates to **12** and then reacts with another molecule of itself to form dimer **2'** or **4'**. Because our results showed that using more T3P equivalents resulted in fewer (Table S3) or no dimers (Table S4), we propose that excess T3P promotes activation of both carboxylate and carbamate groups in **8** to provide **11**. This species can readily convert to **2** or **4** through a yet-unknown pathway that can effectively avoid dimer formation.



Scheme 3. Proposed mechanisms for the formation of NCAs (**2** and **4**) and dimer products (**2'** and **4'**).

To evaluate the greenness of our NCA synthesis method, we performed a qualitative analysis based on the C1 source in the NCA product, toxicity of reagents/reactants/solvents used, and complexity of the purification process (Scheme 4). As benchmarks, we selected several representative examples from the literature in which five-membered ring NCAs were forged from amino acid starting materials. We found that the conventional methods all employed components that directly or indirectly originate from phosgene in their life cycle (e.g., in Method I,[53] bis(2,4-dinitrophenyl)carbonate is prepared from $COCl_2$; in Methods II[22] and III,[54] Boc-protected amino acids are made from Boc_2O that is produced from $COCl_2$) or generate phosgene in situ (e.g., triphosgene in Method III[54]). Furthermore, the need for column chromatography in Method III adds an additional cost in terms of materials consumed and

chemical waste produced. In comparison, our NCA synthesis method (IV) scores favorably because it uses earth abundant CO_2 and provides NCAs with high purity after simple extraction procedures (Scheme 4E). Moreover, T3P is a relatively benign reagent because it can be rapidly degraded in aqueous solutions[55] and its propylphosphonic acid byproduct could be recovered and converted back to T3P.[56] Although our reactions employ acetonitrile, which may be problematic from a toxicology standpoint,[57, 58] we have found that other solvents such as propylene carbonate/tetrahydrofuran (3:2) mixtures can also give good yields (77%, Table S5). We anticipate that further optimization of our NCA synthesis method by testing green solvent alternatives[59, 60] and minimizing use of excess reagents will likely lead to even greater improvements in its health and environmental friendliness.



Method	C1 Source	Toxicity	Purification	Overall
I	●	●	●	● ● ●
II	●	●	●	● ● ●
III	●	●	●	● ● ●
IV	●	●	●	● ● ●

Scheme 4. Comparison of methods available for the preparation of five-membered ring NCAs from amino acids. Boc-protected amino acids (B and C) are derived from Boc_2O, which is generated from the highly toxic gas phosgene. Similarly, bis(2,4-dinitrophenyl)carbonate (A) is also obtained from $COCl_2$. Our NCA synthesis method has moderate toxicity due to the use of acetonitrile. However, greener solvent alternatives could be identified in future optimization studies. See Scheme S5 for more details.

Conclusions

In summary, we developed a phosgene-free strategy to synthesize five- and six-membered ring NCAs directly from amino acids and carbon dioxide. Our mild reaction conditions allowed us to perform tandem reactions for producing tryptanthrin and related alkaloids, which have promising medicinal properties. We found that T3P is key to achieving high selectivity of NCAs over amino acid dimers since other common coupling reagents were either inefficient or ineffective. A qualitative analysis revealed that our NCA synthesis method is advantageous over conventional methods based on multiple green chemistry criteria. Because NCAs have extensive applications, we anticipate that our approach could be used broadly in both small molecule and polymer synthesis.

Author Contributions

T. V. Tran, Y. Shen, H. D. Nguyen, and S. Deng performed experiments and prepared the manuscript. H. Roshandel conducted DFT calculations. M. Cooper and J. R. Watson contributed to synthesis. J. A. Byers offered project suggestions and commented on the manuscript. P. Diaconescu and L. H. Do led the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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