FULL PAPER

Rapid and Mild Lactamization Using Highly Electrophilic Triphosgene in a Micro-Flow Reactor

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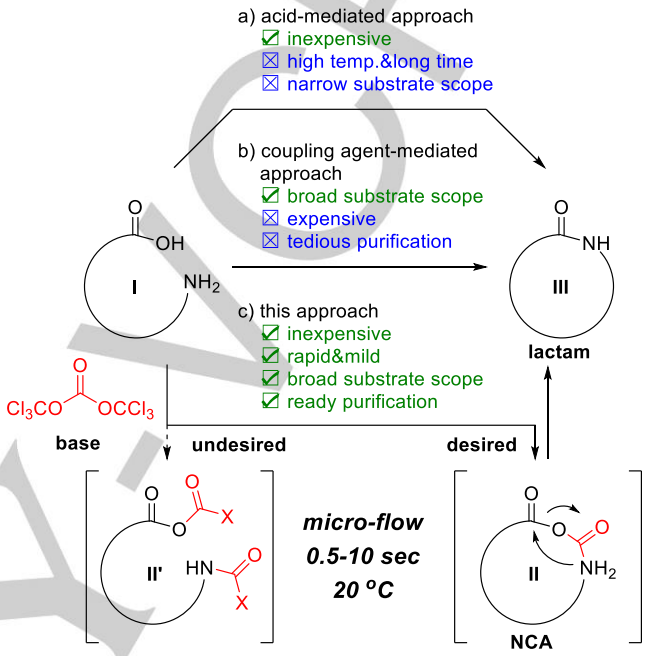
Abstract: Lactams are cyclic amides that are indispensable as drugs and as drug candidates. Conventional lactamization includes acid-mediated approaches and coupling agent-mediated approaches that suffer from a narrow substrate scope, much waste, and/or high cost. Inexpensive, less wasteful and highly electrophilic reagent-mediated approaches are attractive, but there is an imminent risk of side reactions. Herein, we describe methods using highly electrophilic triphosgene in a micro-flow reactor that accomplish lactamization that are rapid (0.5-10 sec), mild, inexpensive, and less wasteful. We developed two methods, referred to here as A and B, using NMM and NMI, respectively. Various lactams as well as a cyclic peptide containing acid- and/or heat-labile functional groups were synthesized in good to high yields without the need for tedious purifications. Undesired reactions were successfully suppressed and the risk in handling triphosgene was minimized by the use of micro-flow technology.

Introduction

Amides are the chemical structure most frequently found in biologically active compounds reported in medicinal chemistry-related journals from 1976 to 2018.[1] In fact, *ca.* 40% of bioactive compounds contain the amide structure. The β- and γ-lactam structures rank 15th and 42nd among the 351 ring systems found for marketed drugs,[2] which is why we stated that cyclic amides are of such importance as drugs and drug candidates. Lactams can be prepared via iodolactamization,[3] Beckmann rearrangement,[4] Schmidt reaction,[5] and Kinugasa reaction.[6] All of these reactions, however, require harsh conditions and/or are limited in the scope of available substrates. Lactamization (**I** to **III**) is the most frequently used process in the synthesis of lactams and can be broadly divided into two groups, as shown in Scheme 1.[7] Acid ($Ti(O\textit{i}\text{-}Pr)_4$,[8] Al_2O_3,[9] $(CF_3CH_2O)_3B$,[10] $ArB(OH)_2$,[11] Bu_2SnO,[12] Et_3Ga,[13] polyoxometalate,[14] and ZSM-5[15]) -mediated approaches that are used for less-functionalized lactam syntheses (Scheme 1a). Although these approaches usually use



Scheme 1. Conventional lactamization approaches a), b); and the developed micro-flow lactamization approach c).

inexpensive reagents, they require high temperature, extended periods of time, and acidic conditions, therefore, which limits the substrate scope. Coupling agent (such as DCC[16], BOP[17], and Mukaiyama reagent[18]) -mediated approaches were used for functionalized lactam syntheses (Scheme 1b). Moderately electrophilic coupling agents usually are used to avoid undesired reactions at the amino group in **I** and racemization. Although these approaches feature a broad substrate scope, they require expensive and wasteful coupling agents that sometimes require tedious systems of purification.

Continuous-flow synthesis has revolutionized synthetic organic chemistry over the past several decades.[19] The risk in handling dangerous compounds can be decreased[20] and scale-up can be easily achieved[21] either by simply extending the running time or increasing the number of reactors. Reaction times (< 1 sec) and temperatures can be precisely controlled due to a short diffusion length and rapid heat transfer of micro-flow reactors (inner diameter ≤ 1 mm).[22] Many sophisticated methods for flow synthesis utilize highly active and unstable compounds, and these cannot be achieved via conventional batch approaches.[23] Therefore, it is important to expand the application of micro-flow approaches to highly active and labile compounds in order to further develop high-yielding, sustainable, and inexpensive synthetic processes.

We have developed synthetic processes using highly active and unstable compounds that cannot be achieved by

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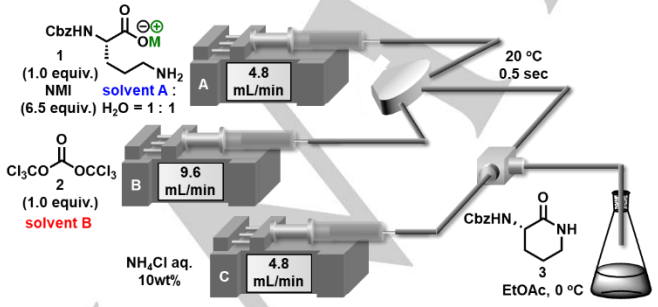
conventional batch approaches[24] and reported the mild and rapid synthesis of linear peptides and amino acid *N*-carboxy anhydrides (NCAs) with 5- and 6-membered rings using highly electrophilic, inexpensive, and less wasteful triphosgene.[24a-d, 25] During the course of the synthesis of a NCA with 7-membered ring **II** from **I**, we coincidentally obtained γ-lactam **III** instead of **II** probably due to a spontaneous ring contraction of **II** (Scheme 1c). In general, the use of highly electrophilic reagents such as triphosgene is risky in lactamization because they easily induce an undesired reaction (**I** to **II'**) and racemization.[26] If the undesired reactions could be suppressed, however, it would be an ideal approach. In the present study we conducted triphosgene-mediated lactamization (Scheme 1c) that was both rapid (0.5-10 sec) and mild. Structurally diverse lactams and a peptide containing acid and/or heat-labile functional groups were synthesized in good to high yields without the need for tedious purifications. The aforementioned undesired reactions were successfully suppressed and the risk in handling toxic gas was minimized by the use of micro-flow technology.

Results and Discussion

Solvents and counter cations were examined in the lactamization of Cbz-protected ornithine **1** (Table 1). A V-shape mixer[27] and a T-shape mixer were connected with a Teflon® tube and the reactor was immersed in a water bath (20 °C). A solution of the alkali metal salt of **1** and an amine base in solvent A and water (1:1) was introduced into the first mixer via syringe pump A. The solution of triphosgene (**2**) in solvent B was also introduced into the first mixer via syringe pump B. The carboxylate was rapidly activated by triphosgene that led to lactamization. An aqueous solution of ammonium chloride was introduced into the second mixer to quench the reaction, and the resultant mixture containing **3** was poured into ethyl acetate at 0 °C. Various solvents can be employed as solvent A (entries 1-5). The use of hydrophilic solvents (MeCN and 1,4-dioxane) was important as solvent B, however, in order to obtain good results probably due to the rapid mixing of organic and aqueous solutions (entries 6-11). Readily removable MeCN was used as both solvents A and B in the following examinations. Counter cations of **1** influenced its solubility and basicity. The use of potassium salts afforded the best results (entries 1 and 12-14).

Table 1. Examination of solvents and counter cations in **1** in micro-flow lactamization.

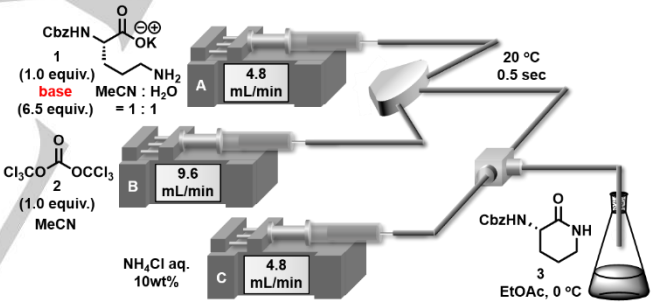


entry	solvent A	solvent B	M	yield[a] [%]
1	MeCN	MeCN	Na	82
2	THF	MeCN	Na	76
3	1,4-dioxane	MeCN	Na	81
4	DMF	MeCN	Na	81
5	DMSO	MeCN	Na	82
6	MeCN	THF	Na	79
7	MeCN	1,4-dioxane	Na	66
8	MeCN	hexane	Na	28
9	MeCN	EtOAc	Na	26
10	MeCN	Et_2O	Na	22
11	MeCN	CH_2Cl_2	Na	7
12	MeCN	MeCN	Li	76
13	MeCN	MeCN	K	84
14	MeCN	MeCN	Cs	76

[a] Yields were determined by HPLC-UV analysis. NMI = *N*-methylimidazole, Cbz = benzyloxycarbonyl, DMF = *N*,*N*-dimethyl formamide, DMSO = dimethyl sulfoxide.

Organic bases were examined as shown in Table 2. The basicity of the amines significantly influenced the results. The use of both a weak base, pyridine (pK_aH < 7), and strong bases, DMAP, *N*-methylpiperidine, and DBU (pK_aH > 9), resulted in

Table 2. Examination of bases and amounts of reagents in micro-flow lactamization.



entry	base (pK_aH[b])	yield[c] [%]
1	pyridine (5.2)[28]	55
2	NMI (7.0)[28]	84
3	NMM (7.4)[29]	90-92[d] (93[e])
4[a]	NMM	73-80[d]
5	*N*-ethylmorpholine (7.7)[29]	65
6	Me_2NBn (8.9)[30]	84
7	DMAP (9.7)[31]	40
8	*N*-methylpiperidine (10.1)[30]	50
9	DBU (11.5)[32]	2

[a] Batch reactions were performed under vigorous stirring (1,000 rpm). Reaction time was 10 sec. [b] The pK_a of conjugated acids. [c] Yields were determined by HPLC-UV analysis. [d] Three independent experiments were carried out. [e] Isolated yield. NMM: *N*-methylmorpholine, Bn: benzyl, DMAP: *N*,*N*- dimethylaminopyridine, DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene.

unsatisfactory yields (≤ 50%, entries 1 and 7-9), whereas the use of moderately basic amines (7 ≤ pK_aH ≤ 9) afforded higher yields (entries 2, 3, 5 and 6). NMM and *N*-methylpiperidine have almost the same steric bulkiness, and the obvious difference in the yields between the two clearly indicates the importance of basicity in this reaction (entry 3 vs. 8). The nucleophilicity of amines is also important in this reaction. Although *N*-ethylmorpholine (pK_aH = 7.7) and NMM (pK_aH = 7.4) have similar basicity, the less nucleophilic *N*-ethylmorpholine afforded a lower yield (entry 5) compared with that of NMM (entry 3). In order to verify the importance of the micro-flow conditions, comparative batch conditions were examined under the same reaction conditions with the exception of reaction time (10 sec), because it was impossible to perform the batch reaction in 0.5 sec (entry 4). Although the reaction mixture was vigorously stirred during the experiments, reproducible results were not observed due to batch-to-batch differences in the mixing efficiency. Observed yields under batch conditions were lower than those under flow conditions (entry 3 vs. 4). In addition, special care should be taken due to evolution of large amounts of gas such as HCl, CO_2 and phosgene, therefore scale-up of the reaction using a batch reactor should be avoided. On the other hand, micro-flow experiments were performed safely, and more reproducible results were obtained. It is noteworthy that no racemization was observed under the optimized conditions of entry 3 (for details, see Supporting Information) although highly electrophilic triphosgene was used. A plausible reaction mechanism is offered in Scheme 3.

The conditions of entry 3 (= method A) afforded highly pure lactam **3** only by simple phase separation purification. The observed ^{1}H NMR spectrum of **3** appears in Figure 1. Method A was used for a later examination of the substrate scope.[33]

Next, we examined lactamization of the Cbz-protected lysine **4** (Table 3). Unexpectedly, the optimized conditions (method A) resulted in a low yield (35%, entry 1). We examined organic bases once again (for details, see Supporting Information). As a result, the less-basic (pK_aH = 7.0) nucleophilic NMI afforded the best results for the lactamization of **4** (entry 2). Extension of the reaction time and increase in temperature slightly improved the yield (entries 2-4). The comparative batch conditions afforded similar yields, although special care should be taken due to the evolution of large amounts of toxic gas (entry 5). To our delight, no racemization was observed in the ε-lactam formation under the optimized conditions of entry 4 (for details, see Supporting Information). A plausible reaction mechanism is offered in Scheme 3. Thus, conditions of entry 4 (= method B) were also used for a following examination of the substrate scope.[34]

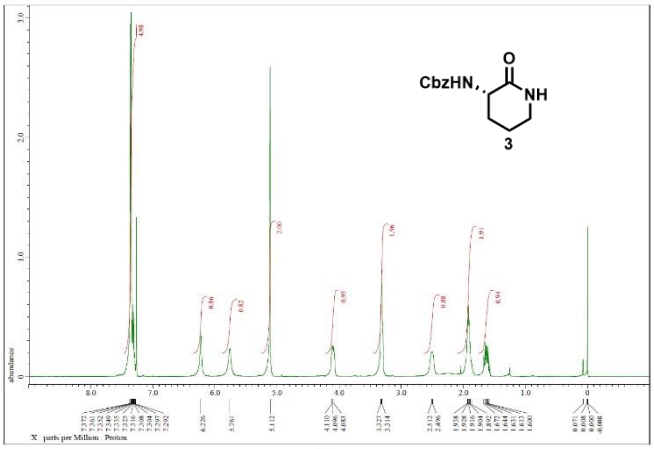
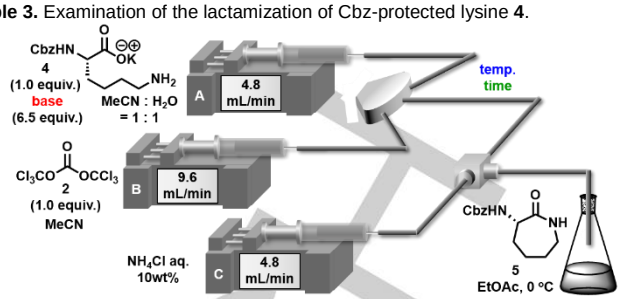


Figure 1. ^{1}H NMR spectrum of lactam **3** after phase separation.

Table 3. Examination of the lactamization of Cbz-protected lysine **4**.



entry	base (pK_aH [b])	time [sec]	temp. [°C]	yield[c] [%]
1	NMM (7.4)	0.5	20	35
2	NMI (7.0)	0.5	20	52
3	NMI	10	20	58
4	NMI	10	60	61-63[c] (72[d])
5[a]	NMI	10	60	61-62[e]

[a] Batch reactions were performed under vigorous stirring (1,000 rpm). Reaction time was 10 sec. [b] The pK_a of conjugated acids. [c] Yields were determined by HPLC-UV analysis. [d] Isolated yield. [e] Three independent experiments were carried out.

The substrate scope was examined using developed methods A and B (Figure 2). Readily cyclizable γ-lactams **6**-**9** as well as

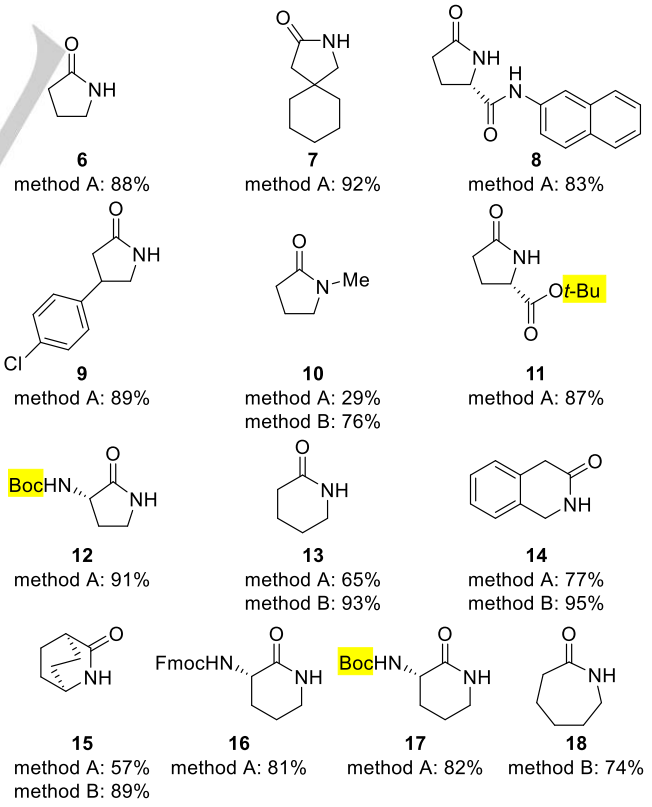
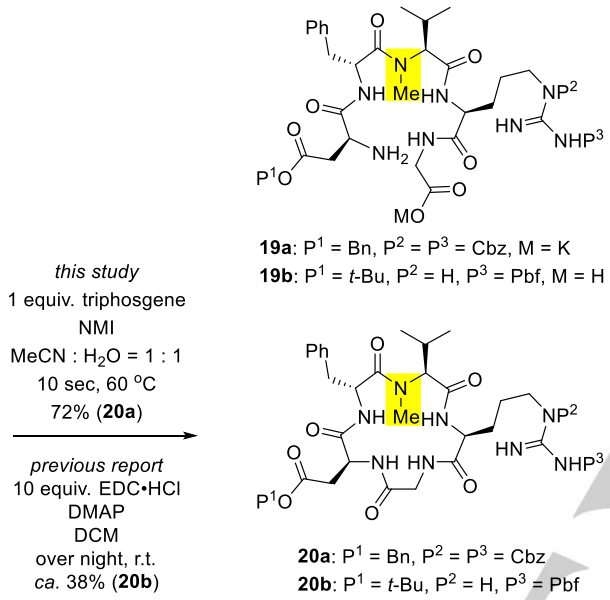


Figure 2. Substrate scope of the developed micro-flow lactamization. Isolated yields are shown. Labile functional groups are highlighted in yellow.

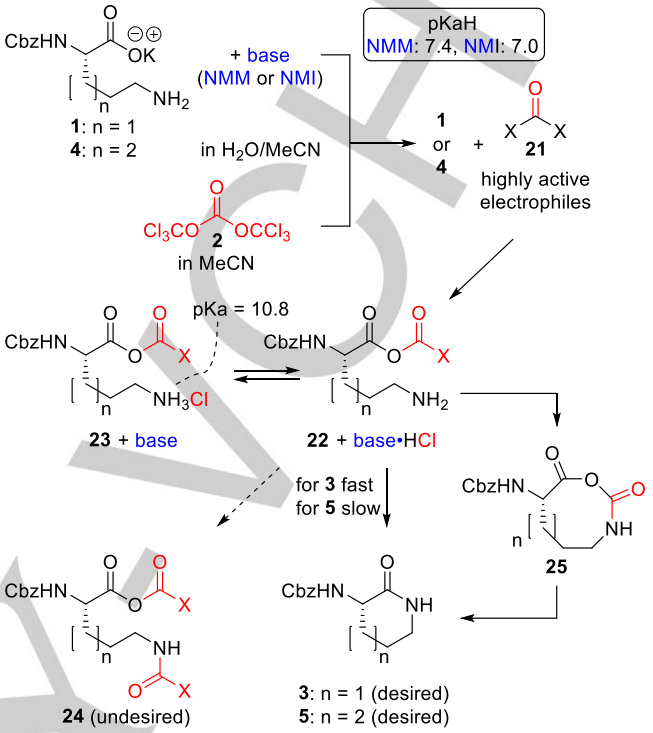
11 and **12** were prepared in high yields via method A. On the other hand, in the case of *N*-methylpyrrolidone (**10**), method B was preferable probably due to a slower rate of cyclization, which was caused by the bulky NMe group. In the case of δ-lactams, interestingly, ornithines **16** and **17** were obtained in high yields via method A. In the case of **13**-**15**, however, method B was preferable. Method B was used to prepare ε-caprolactam (**18**) in a good yield. It is noteworthy that acid- and/or heat-labile *t*-butyl (*t*-Bu) ester and the Boc group tolerated the developed conditions. In all cases, simple phase separation and/or silica-gel column chromatography afforded the highly pure lactams, and did not require tedious purification.



Scheme 2. Macrolactamization for the synthesis of protected cilengitide **20**. Labile functional groups are highlighted in yellow. EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, Pbf: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl.

The developed method B was applied to cyclic RGD peptide (protected cilengitide **20**[35]) synthesis.[36] Reportedly, macrolactamization of **19b** using 10 equiv. of EDC· HCl (r.t., over night) afforded the desired **20b** in *ca.* 38% yield (Scheme 2).[37] On the other hand, our developed conditions afforded the desired **20a** in 72% yield from **19a** (for preparation details, see Supporting Information) only in 10 sec, although **20a** contained an acid-labile *N*-methyl amide structure (Scheme 2).

A plausible reaction mechanism appears in Scheme 3. We speculated that highly active electrophiles **21** such as phosgene and acyl ammonium or acyl *N*-methyl imidazolium cation were generated from the reaction between triphosgene (**2**) and various nucleophiles including carboxylates (**1** or **4**), a base, and water. The coupling of **1** or **4** with **21** rapidly afforded **22**. Then, a proton exchange between **22** and an organic base occurred. The equilibrium between **22** and **23** prevented an undesired coupling (**22** to **24**). It is conceivable that the use of moderately basic NMM (pK_aH = 7.4) or NMI (pK_aH = 7.0) was important for controlling the equilibrium (pKa of hydrochloric salt **23**: *ca.* 10.8[38]). Direct lactamization and/or formation of NCA **25** and the subsequent ring contraction from **22** afforded the desired lactams **3** and **5**. Although it is unclear why method A is suitable for **3** and method B is suitable for **5**, the differences in basicity and nucleophilicity between NMM (method A) and NMI (method B) could have influenced the equilibrium between **22** and **23**, and/or the reaction pathway (direct lactamization or NCA formation).



Scheme 3. Plausible reaction mechanism of triphosgene-mediated lactamization.

Conclusion

In conclusion, we described a lactamization process that is rapid (0.5-10 sec) and mild, and is accomplished via the use of triphosgene in a micro-flow reactor. We developed NMM- (method A) and NMI-mediated conditions (method B). Various lactams as well as a cyclic peptide containing acid- and/or heat-labile functional groups were synthesized in good to high yields. In addition, the desired compounds were obtained without tedious purifications. In lactamization, the use of highly electrophilic reagents is usually avoided due to high risk of side reactions. These undesired reactions were successfully avoided and the risk in handling toxic gas was minimized by the use of micro-flow technology. The developed methodology should be valuable for accelerating drug development based on various lactams.

Experimental Section

Typical procedure for synthesis of lactam 3 using a micro-flow reactor: method A

A solution of **amino acid 1** (0.100 M, 0.48 mmol, 1.00 equiv.), *N*-methylmorpholine (0.650 M, 6.50 equiv.), and 2 M KOH (0.100 M, 1.00 equiv.) in H_2O and MeCN (1 : 1) (flow rate: 4.80 mL/min) and a solution of triphosgene (0.0500 M, 1.00 equiv.) in MeCN (flow rate: 9.60 mL/min) were introduced to V-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.800 mm,

length: 239 mm, volume: 120 µL, reaction time: 0.500 sec) at the same temperature. The resultant mixture and 10 wt% NH_4Cl aq. (flow rate: 4.80 mL/min) were introduced to T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.800 mm, length: 433 mm, volume: 218 µL, reaction time: 0.680 sec) at the same temperature. After being eluted for *ca*. 15 sec to reach a steady state, the resultant mixture was poured into EtOAc (5 mL) for 35 sec at 0 °C. The organic layer was washed three times with 1 M HCl (1 mL). After the aqueous layer was extracted three times with EtOAc (2 mL), the organic layer was washed with 1 M HCl (1 mL), sat. $NaHCO_3$ aq. (1 mL), and brine (1 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. The desired lactam **lactam 3** was obtained in 93% yield

Benzyl (*S*)-(2-oxopiperidin-3-yl)carbamate (3) was obtained as white solids. mp: 82-84 °C; $[\alpha]^{26}_D$ = -17.5 (c 1.11, MeOH); IR (neat): 3303, 3063, 2948, 1714, 1670, 1495, 1300, 1045, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 6.23 (s, 1H), 5.76 (s, 1H), 5.11 (s, 2H), 4.10 (t, *J* = 5.5 Hz, 1H), 3.32 (d, *J* = 5.0 Hz, 2H), 2.50 (d, *J* = 6.4 Hz, 1H), 1.94-1.86 (m, 2H), 1.67-1.57 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 156.5, 136.5, 128.6, 128.2, 66.9, 51.9, 41.9, 27.8, 21.2. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[39]

Typical procedure for synthesis of lactam 5 using a micro-flow reactor: method B

A solution of **amino acid 4** (0.100 M, 0.48 mmol, 1.00 equiv.), *N*-methylimidazole (0.650 M, 6.50 equiv.), and 2 M KOH (0.100 M, 1.00 equiv.) in H_2O and MeCN (1 : 1) (flow rate: 4.80 mL/min) and a solution of triphosgene (0.0500 M, 1.00 equiv.) in MeCN (flow rate: 9.60 mL/min) were introduced to V-shape mixer at 60 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.800 mm, length: 4776 mm, volume: 2400 µL, reaction time: 10.0 sec) at the same temperature. The resultant mixture and 10 wt% NH_4Cl aq. (flow rate: 4.80 mL/min) were introduced to T-shape mixer at 60 °C with the syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.800 mm, length: 433 mm, volume: 218 µL, reaction time: 0.680 sec) at the same temperature. After being eluted for *ca*. 25 sec to reach a steady state, the resultant mixture was poured into EtOAc (5 mL) for 25 sec at 0 °C. The organic layer was washed three times with 1 M HCl (1 mL). After the aqueous layer was extracted three times with EtOAc (2 mL), the organic layer was washed with 1 M HCl (1 mL), sat. $NaHCO_3$ aq. (1 mL), and brine (1 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **lactam 5** was obtained in 72% yield.

Benzyl (*S*)-(2-oxoazepan-3-yl)carbamate (5) was obtained as white solids. mp: 119-122 °C; IR (neat): 3247, 3091, 2930, 1721, 1668, 1497, 1213, 1051, 744; $[\alpha]^{25}_D$ = -1.3 (c 1.46, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 6.70 (brs, 1H), 6.20 (brs, 1H), 5.13-5.06 (m, 2H), 4.33 (dd, *J* = 6.0, 10.1 Hz, 1H), 3.24-3.21 (m, 2H), 2.11-1.98 (m, 2H), 1.83-1.72 (m, 2H), 1.57-1.47 (m, 1H), 1.42-1.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 155.6, 136.7, 128.6, 128.1, 128.1, 66.7, 53.7, 42.2, 32.1, 28.9, 28.1. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[40]

Pyrrolidin-2-one (6)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and DCM, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **Pyrrolidin-2-one** was obtained in 88% yield as colorless oil. IR (neat): 3249, 2891, 1684, 1464, 1426, 1286; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 3.37 (t, *J* = 7.1 Hz, 2H), 2.27 (t, *J* = 8.0 Hz, 2H), 2.1 (quint, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.5, 42.4, 30.2, 20.9. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[41]

2-Azaspiro[4.5]decan-3-one (Gabapentin-lactam) (7)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **Gabapentin-lactam** was obtained in 92% yield as white solids. mp: 84-86 °C; IR (neat): 3195, 3092, 2924, 2854, 1689, 1446, 1380; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 3.11 (s, 2H), 2.13 (s, 2H), 1.52-1.35 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 53.8, 43.3, 39.5, 36.9, 25.7, 22.9; HRMS (ESI): calcd for $[C_9H_{15}NO+Na]^+$ 176.1046, found 176.1046.

(*S*)-*N*-(Naphthalen-2-yl)-5-oxopyrrolidine-2-carboxamide (8)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and DCM, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **(*S*)-*N*-(Naphthalen-2-yl)-5-oxopyrrolidine-2-carboxamide** was obtained in 83% yield as white amorphous solids. $[\alpha]^{26}_D$ = -11.6 (c 0.72, $CHCl_3$); IR (neat): 3276, 3058, 1693, 1588, 1434, 1257, 749; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.26 (s, 1H), 8.32 (d, *J* = 1.4 Hz, 1H), 7.94 (s, 1H), 7.89-7.81 (m, 3H), 7.63 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.49-7.39 (m, 2H), 4.26 (dd, *J* = 4.1, 8.7 Hz, 1H), 2.42-2.33 (m, 1H), 2.30-2.12 (m, 2H), 2.08-2.01 (m, 1H**);** ^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 177.5, 171.6, 136.4, 133.4, 129.9, 128.4, 127.5, 127.3, 126.5, 124.7, 120.0, 115.6, 56.5, 29.3, 25.4; HRMS (ESI): calcd for $[C_{15}H_{14}N_2O_2+Na]^+$ 277.0947, found 277.0948.

4-(4-Chlorophenyl)pyrrolidin-2-one (Baclofen-lactam) (9)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **Baclofen-lactam** was obtained in 89% yield as white solids. mp 115-118 °C; IR (neat): 3197, 3094, 2880, 1693, 1491, 1260, 812; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.14 (m, 5H), 3.79 (t, *J* = 8.9 Hz, 1H), 3.70-3.62 (m, 1H), 3.39 (dd, *J* = 6.9, 9.6 Hz, 1H), 2.74 (dd, *J* = 8.7, 16.9 Hz, 1H), 2.45 (dd, *J* = 8.5, 16.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 140.8, 132.9, 129.0, 128.2, 49.6, 39.7, 38.1. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[42]

1-Methylpyrrolidin-2-one (10)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **1-Methylpyrrolidin-2-one** was obtained in 29% yield as colorless oil. **Reaction conditions:** Method B; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **1-Methylpyrrolidin-2-one** was obtained in 76% yield as colorless oil. IR (neat): 2923, 1680, 1505, 1300; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38-3.34 (m, 2H), 2.82 (s, 3H), 2.35 (t, *J* = 8.0 Hz, 2H), 2.04-1.96 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.2, 49.5, 30.8, 29.7, 17.8. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[43]

***tert*-Butyl (*S*)-5-oxopyrrolidine-2-carboxylate (11)**

Reaction conditions: Method A; **Work up:** The organic layer was washed three times with 1 M HCl (1 mL). After the aqueous layer was extracted three times with EtOAc (2 mL), the organic layer was washed with 1 M HCl (1 mL), sat. $NaHCO_3$ aq. (1 mL), and brine (1 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. ***tert*-Butyl (*S*)-5-oxopyrrolidine-2-carboxylate** was obtained in 87% yield as white solids. mp: 101-103 °C; IR (neat): 3236, 2975, 1735, 1690, 1452, 1229; $[\alpha]^{26}_D$ = -0.6 (c 2.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (brs, 1H), 4.11 (dd, *J* = 5.3, 8.0 Hz, 1H), 2.45-2.25 (m, 3H), 2.18-2.10 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.1, 171.2, 82.4, 56.2, 29.5, 28.0, 24.9; HRMS (ESI): calcd for $[C_9H_{15}NO_3+Na]^+$ 208.0944, found 208.0942.

tert-Butyl (*S*)-(2-oxopyrrolidin-3-yl)carbamate (12)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). ***t*ert-Butyl (*S*)-(2-oxopyrrolidin-3-yl)carbamate** was obtained in 91% yield as white solids. mp: 171-174 °C; IR (neat): 3324, 2978, 2931, 1696, 1530, 1294, 1170; $[\alpha]^{26}_D$ = +3.9 (c 2.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H), 5.26 (s, 1H), 4.14 (s, 1H), 3.36-3.25 (m, 2H), 2.61 (s, 1H), 2.00-1.87 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 156.0, 79.9, 51.8, 39.2, 30.2, 28.4. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[44]

Piperidin-2-one (13)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and DCM, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **Piperidin-2-one** was obtained in 65% yield as colorless oil. **Reaction conditions:** Method B; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and DCM, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **Piperidin-2-one** was obtained in 93% yield as colorless oil. IR (neat): 3232, 2944, 2869, 1663, 1496, 1353; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (brs, 1H), 3.29 (t, *J* = 5.3 Hz, 2H), 2.33 (t, *J* = 6.2 Hz, 2H), 1.81-1.70 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 42.3, 31.6, 22.3, 20.9. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[45]

1,4-Dihydroisoquinolin-3(2*H*)-one (14)

Reaction conditions: Method A; **Work up:** The organic layer was washed three times with 1 M HCl (1 mL). After the aqueous layer was extracted three times with EtOAc (2 mL), the organic layer was washed with 1 M HCl (1 mL), sat. $NaHCO_3$ aq. (1 mL), and brine (1 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. **1,4-Dihydroisoquinolin-3(2*H*)-one** was obtained in 77% yield as white solids. **Reaction conditions:** Method B; **Work up:** The organic layer was washed three times with 1 M HCl (1 mL). After the aqueous layer was extracted three times with EtOAc (2 mL), the organic layer was washed with 1 M HCl (1 mL), sat. $NaHCO_3$ aq. (1 mL), and brine (1 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **1,4-Dihydroisoquinolin-3(2*H*)-one** was obtained in 95% yield as white solids. mp: 145-147 °C; IR (neat): 3191, 3042, 1658, 1497, 1349, 837, 743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (brs, 1H), 7.28-7.16 (m, 4H), 4.51 (s, 2H), 3.59 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 131.7, 131.1, 127.8, 127.5, 126.7, 125.4, 45.3, 36.5. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[46]

(1*S*,4*S*)-2-Azabicyclo[2.2.2]octan-3-one (15)

Reaction conditions: Method A; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **(1s,4s)-2-Azabicyclo[2.2.2]octan-3-one** was obtained in 58% yield as white solids. **Reaction conditions:** Method B; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **(1s,4s)-2-Azabicyclo[2.2.2]octan-3-one** was obtained in 89% yield as white solids. mp: 135-138 °C; IR (neat): 3181, 3083, 2954, 2871, 1678, 1450, 1273, 1105; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H), 3.60 (s, 1H), 2.47 (s, 1H), 1.82-1.57 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.7, 47.5, 37.7, 27.6, 24.0. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[47]

(9*H*-Fluoren-9-yl)methyl (*S*)-(2-oxopiperidin-3-yl)carbamate (16)

Reaction conditions: Method A; **Work up:** After being eluted for *ca*. 15 sec to reach a steady state, the resultant mixture was poured into EtOAc (20 mL) for 35 sec at 0 °C. The aqueous layer was extracted three times with EtOAc (3 mL). The organic layer was washed with NaCl in 1 M HCl aq. (3 mL), brine (3 mL), sat. $NaHCO_3$ aq. (3 mL), and brine (3 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. **(9*H*-Fluoren-9-yl)methyl (*S*)-(2-oxopiperidin-3-yl)carbamate** was obtained in 81% yield as white amorphous solids. $[\alpha]^{25}_D$ = +37.9 (c 1.14, $CHCl_3$); IR (neat): 3296, 2947, 1712, 1670, 1493, 1247, 758, 741; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.61 (d, *J* = 5.5 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 6.39 (s, 1H), 5.86 (s, 1H), 4.37 (d, *J* = 5.0 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.11 (brs, 1H), 3.32 (brs, 2H), 2.51 (brs, 1H), 1.92 (brs, 2H), 1.65 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 156.5, 144.1, 144.0, 141.4, 127.8, 127.2, 125.3, 120.0, 67.1, 51.9, 47.3, 41.8, 27.7, 21.1; HRMS (ESI): calcd for $[C_{20}H_{20}N_2O_3+Na]^+$ 359.1366, found 359.1370.

***tert*-Butyl (*S*)-(2-oxopiperidin-3-yl)carbamate (17)**

Reaction conditions: Method A; **Work up:** After being eluted for *ca*. 15 sec to reach a steady state, the resultant mixture was poured into EtOAc (20 mL) for 35 sec at 0 °C. The aqueous layer was extracted three times with EtOAc (3 mL). The organic layer was washed with sat. NaCl-containing 1 M HCl aq. (3 mL), brine (3 mL), sat. $NaHCO_3$ aq. (3 mL), and brine (3 mL) at room temperature, dried over $MgSO_4$, filtered and evaporated. ***tert*-Butyl (*S*)-(2-oxopiperidin-3-yl)carbamate** was obtained in 82% yield as colorless oil. $[\alpha]^{26}_D$ = -9.7 (c 0.83, MeOH); IR (neat): 3303, 2975, 1703, 1672, 1493, 1248, 1168; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 5.49 (d, *J* = 4.6 Hz, 1H), 4.00 (brt, *J* = 5.5 Hz, 1H), 3.31-3.27 (m, 2H), 2.43 (brd, *J* = 6.9 Hz, 1H), 1.94-1.76 (m, 2H), 1.63-1.53 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 156.0, 79.7, 51.5, 41.8, 28.4, 27.9, 21.1. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[48]

Azepan-2-one (18)

Reaction conditions: Method B; **Work up:** After removing the solvent by evaporation, the reaction mixture was dissolved in THF and $CHCl_3$, the solid was removed by filtration, the solution was collected, and then the solvent was removed. The reaction mixture was purified by silica gel column chromatography (MeOH : DCM = 1 : 9). **Azepan-2-one** was obtained in 74% yield as white solids. mp: 67-68 °C; IR (neat): 3294, 3206, 2927, 1660, 1486, 1417, 1364, 1290; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 3.18 (dd, *J* = 5.7, 9.8 Hz, 2H), 2.44 (t, *J* = 5.5 Hz, 2H), 1.76-1.60 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.4, 42.9, 36.9, 30.7, 29.8, 23.3. Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported.[49]

Protected cilengitide 20a

Reaction conditions: Method B (substrate concentration: 0.0100 M); A solution of **pentapeptide hydrochloride S-13** (0.0100 M, 1.00 equiv.), *N*-methylimidazole (0.0650 M, 6.50 equiv.), and 2 M KOH (0.0200 M, 2.00 equiv.) in H_2O and MeCN (1 : 1) (flow rate: 4.80 mL/min) and a solution of triphosgene (0.00500 M, 1.00 equiv.) in MeCN (flow rate: 9.60 mL/min) were introduced to V-shape mixer at 60 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.800 mm, length: 4776 mm, volume: 2400 µL, reaction time: 10.0 sec) at the same temperature. The resultant mixture and 10 wt% NH_4Cl aq. (flow rate: 4.80 mL/min) were introduced to T-shape mixer at 60 °C with the syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.800 mm, length: 433 mm, volume: 218 µL, reaction time: 0.680 sec) at the same temperature. After being eluted for *ca*. 25 sec to reach a steady state, the resultant mixture was poured into EtOAc (20 mL) for 25 sec at 0 °C. **Work up:** The precipitate was washed with MeCN and collected by decantation. **Protected cilengitide** was obtained in 72% yield as white solids. mp: 189-192 °C; IR (neat): 3288, 2929, 1724, 1644, 1535, 1255, 1004, 750; $[\alpha]^{26}_{D}$ = -44.3 (c 0.0780, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 2H), 8.44 (d, *J* = 8.3 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.48-7.50 (m, 1H), 7.28-7.42 (m, 15H), 7.14-7.24 (m, 5H), 5.22 (d, *J* = 2.3 Hz, 2H), 5.03-5.11 (m, 4H), 4.93 (td, *J* = 5.8, 8.7 Hz, 1H) 4.56 (q, *J* = 7.5 Hz, 1H), 4.33 (d, *J* = 10.9 Hz, 1H), 3.72-3.91 (m, 4H), 3.29 (d, *J* = 3.1 Hz, 1H), 3.01 (dd, *J* = 9.1, 13.2 Hz, 1H), 2.86 (dd, *J* = 7.6, 16.3 Hz, 1H), 2.70-2.77 (m, 4H), 2.57-2.63 (m, 1H), 1.84-1.93 (m, 1H), 1.77 (q, *J* = 7.8 Hz, 2H), 1.47-1.58 (m, 3H), 0.73 (d, *J* = 6.5 Hz, 3H) 0.41 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.0, 170.8, 170.0, 169.6, 169.2, 169.1, 162.8, 159.5, 154.9, 137.3, 137.0, 136.0, 135.2, 129.0, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.7, 127.7, 127.7, 127.6, 126.2, 68.1, 66.0, 65.5, 62.8, 54.2, 50.2, 49.1, 44.3, 43.3, 37.8, 34.5, 30.2, 25.8, 25.6, 19.1, 18.9; HRMS (ESI): calcd for $[C_{50}H_{58}N_8O_{11}+Na]^+$ 969.4117, found 969.4118.

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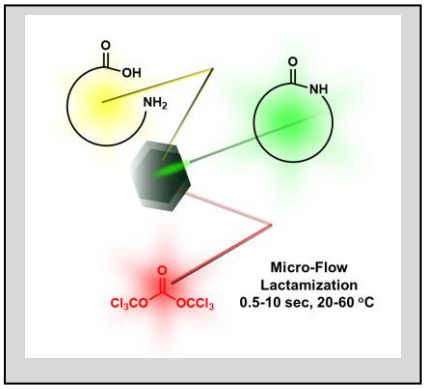

We describe methods that accomplish rapid (0.5-10 sec) and mild lactamizations using highly electrophilic triphosgene in a micro-flow reactor. Various lactams as well as a cyclic peptide containing acid- and/or heat-labile functional groups were synthesized in good to high yields (72-95%). The developed approach enabled a safe, rapid, mild, inexpensive, and less wasteful synthesis of lactams without the need for tedious purifications.