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Graphical Abstract

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One-Pot and Regioselective Synthesis of Functionalized *γ*-lactams via a Metal-Free Sequential Ugi 4CR/Intramolecular 5-*exo*-*dig* Cyclization Reaction

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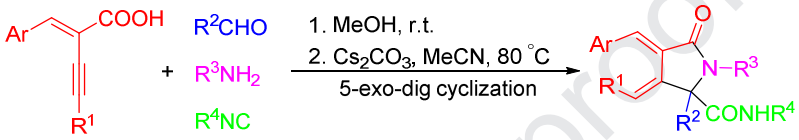

♣ Metal-free reaction
♣ High atom efficiency
♣ Complete regioselectivity
♣ Mild reaction conditions

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One-Pot and Regioselective Synthesis of Functionalized γ-lactams via a Metal-Free Sequential Ugi 4CR/Intramolecular 5-*exo-dig* Cyclization Reaction

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ABSTRACT

A new one-pot and regioselective synthesis of functionalized γ-lactams by a metal-free Ugi 4CR/intramolecular 5-*exo-dig* cyclization sequence under mild conditions has been developed. The reaction of propenoic acid, aldehydes, amines, and isocyanides produced γ-lactams regioselectively in 72-89% yields via sequential Ugi 4CR/intramolecular 5-*exo-dig* cyclization reaction in the presence of Cs_2CO_3.

1. Introduction

Owing to the advantages of rendering sufficient structural diversity, molecule complexity, high atom economy, exceptional efficiency, and convenient one-pot operation, multicomponent reactions (MCRs) have gained extreme popularity in drug discovery, natural products synthesis, biology and material science[1]. Among the variants of MCRs, isocyanide-based multicomponent reactions (IMCRs) have been a practical venue to access diverse highly valuable molecules[2]. In particular, the Ugi four-component reaction (Ugi 4CR) has been widely investigated in organic chemistry for a long history since its first discovery[3]. In addition, the combination of Ugi 4CR with appropriate post-transformations has been a superior tool for the synthesis of functionalized heterocyclic compounds[4]. In our previous work, the sequential Ugi/aza-Wittig, Ugi/Wittig and Ugi/intramolecular alkyne-azide cycloaddition (IAAC) reaction have prepared multisubstituted [1,2,3]-triazolo[1,5-a]-quinoxalin-4(5*H*)-ones, quinoxalin-2(1*H*)-ones, indoles and benzimida-zoles[5].

γ-lactam and its derivatives have been found as a privileged skeleton in a large number of natural products and important pharmaceutical agents (Figure 1)[6]. They often possess a wide array of pharmacological activities, like antiviral[7], cytotoxic[8], anti-inflammatory[9] and antimicrobial[10]. Consequently, consi

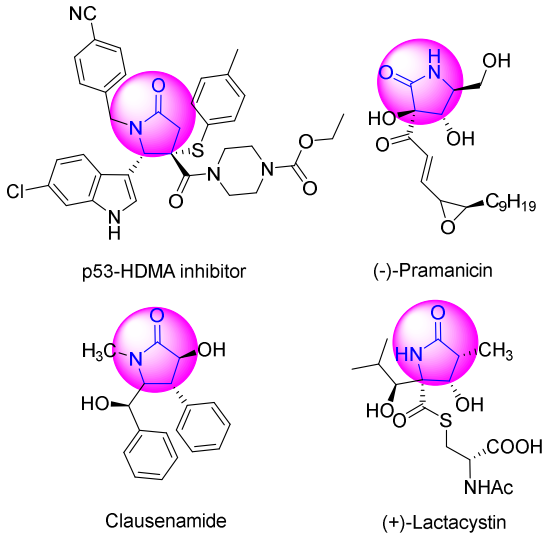

Figure 1. Examples of some biologically important molecules containing γ-lactam motifs.

-derable research efforts have been focused on the development of the synthesis of γ-lactams. The traditional synthetic method for the construction of γ-lactam is based on the cyclization of the dialkyl and primary amines[11]. Moreover, other approaches also

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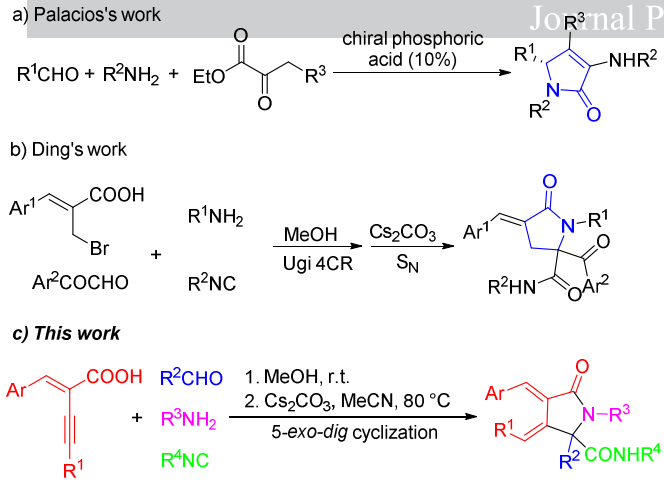


Scheme 1 Approaches of MCRs to *γ*-lactam

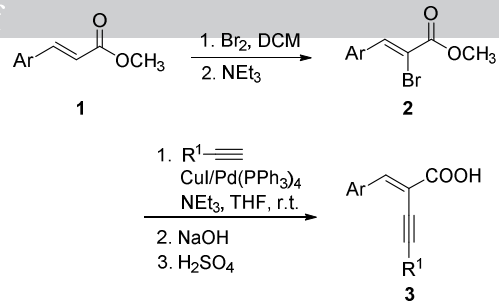
have been reported, such as the expansion of *β*-lactams[12], radical addition-cyclization reaction [13], cycloaddition reaction[14], formation [3+2] annulations[15], metal carbenoid C-H insertion reaction[16] and transition-metal-catalyzed intramolecular allylic alkylation reaction[17]. Although these approaches provide complementary strategies to *γ*-lactams, it should be noted that they suffer from low efficiency, metal contamination of the products and a lack of diversity.

Recently, MCRs have enabled rapid metal-free access to highly functionalized *γ*-lactams with amplified molecular complexity starting from readily available compounds. Pdacios and co-workers documented the first highly enantioselective three-component reaction of pyruvate derivatives, amines and aldehydes to efficiently afforded 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones (Scheme 1a)[18]. Ding's group developed a facile synthesis of 5-oxopyrrolidine-2-carboxamides via Ugi 4CR/S_N cyclization starting from Baylis-Hillman bromides (Scheme 1b) [19]. Despite the remarkable advances, it is still highly desirable to develop a novel, metal-free and robust methodology to construct *γ*-lactams with amplified molecular complexity from readily available starting materials based on MCRs.

In recent years, intramolecular cyclization reaction of alkynes which involved the addition of a nucleophile to carbon-carbon triple bonds to form C-C, C-O, C-N bond have been used for the synthesis of a variety of biologically interesting heterocycles[20]. The combination of Ugi 4CR with a following intramolecular cyclization of alkynes has attracted considerable attention for the construction of diverse heterocyclic scaffolds[21]. Continuing our interest in the development of new strategies for the synthesis of biologically relevant compounds utilizing sequential Ugi 4CR /intramolecular cyclization of alkynes, herein we wish to report a one-pot two-step, metal-free, efficient and atom economical protocol for the regioselective synthesis of functionalized *γ*-lactams through intramolecular 5-*exo*-*dig* cyclization of the Ugi adduct under basic conditions (Scheme 1c). To the best of our knowledge, there is no report previously on the sequential Ugi 4CR/intramolecular cyclization to prepare *γ*-lactams regio-selectively by using propenoic acid as acid component in the Ugi reaction. It is interesting that in spite of Ugi 4CR product comprises multiple nucleophilic centers and two electrophilic sites, the reaction was completely regioselective and provided only *γ*-lactams.

2. Results and discussion

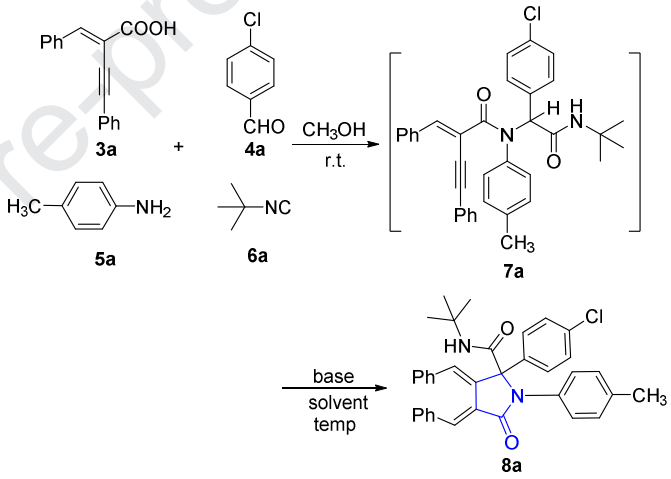
The propenoic acid **3** were prepared as illustrated in Scheme **2**. Bromination of the (E)-methyl cinnamates **1** with Br_2, follow-



Scheme 2 Preparation of propenoic acid **3**

ed by removing HBr with NEt_3, gave (Z)-methyl-2-bromo-3-arylacrylates **2**. Subsequently, a Pd(0) and Cu(I)-catalyzed coupling reaction of compounds (Z)-methyl-2-bromo-3-arylacrylates **2** with 1-alkynes under the Sonogashira conditions and successive hydrolysis reaction were performed. Then, the addition of diluted H_2SO_4 to the reaction mixture to obtain the propenoic acid **3**[22].

In the outset of our study, (E)-2-benzylidene-4-phenylbut-3-ynoic acid (**3a**), 4-chlorobenzaldehyde (**4a**), *p*-methylaniline (**5a**) and *tert*-butylisocyanide (**6a**) were chosen as standard substrates



Scheme 3 Regioselective preparation of compound **8a**

Table 1 Optimization of reaction conditions for the regioselective synthesis of compound **8a**[a]

Entry	Base	solvent	Temp (°C)	Yield (%)[b]
1	-	MeCN	80	0
2	NEt_3	MeCN	80	0
3	$NaHCO_3$	MeCN	80	0
4	K_2CO_3	MeCN	80	50
5[c]	K_2CO_3	MeCN	80	70
6	***Cs_2CO_3***	***MeCN***	***80***	***85***
7[d]	Cs_2CO_3	MeCN	80	75
8	K^tOBu	MeCN	80	40
9	Cs_2CO_3	DMF	80	77
10	Cs_2CO_3	THF	70	60
11	Cs_2CO_3	toluene	110	0

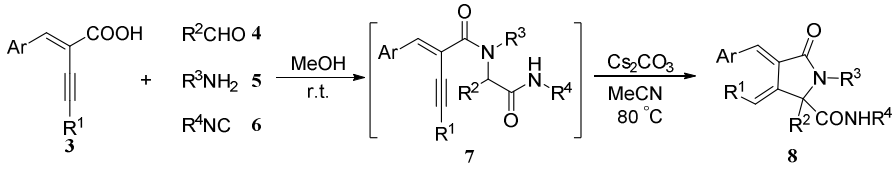
[a] Standard conditions: (E)-2-benzylidene-4-phenylbut-3-ynoic acid **3a** (1 mmol), 4-chlorobenzaldehyde **4a** (1 mmol), *p*-methyl-aniline **5a** (1 mmol), *tert*-butylisocyanide **6a** (1 mmol), base (1 mmol), solvent (5 mL), 4-5 h.

[b] Isolated yield based on (E)-2-benzylidene-4-phenylbut-3-ynoic acid **3a**.

[c] K_2CO_3 (3 mmol)

[d] Cs_2CO_3 (3 mmol)

Table 2 Regioselective synthesis of *γ*-Lactams **8** via a metal-free Sequential Ugi 4CR/intramolecular 5-*exo-dig* cyclization reaction[a]



Entry		Ar	R^1	R^2	R^3	R^4	Yield (%)[b]
1	**8a**	Ph	Ph	4-ClC_6H_4	4-$CH_3C_6H_4$	*t*-Bu	85
2	**8b**	Ph	Ph	4-ClC_6H_4	4-ClC_6H_4	*t*-Bu	75
3	**8c**	Ph	Ph	4-ClC_6H_4	4-BrC_6H_4	*t*-Bu	72
4	**8d**	Ph	4-$CH_3C_6H_4$	Ph	4-$CH_3C_6H_4$	*t*-Bu	84
5	**8e**	Ph	Ph	4-ClC_6H_4	C_6H_5	*t*-Bu	81
6	**8f**	Ph	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$	*t*-Bu	88
7	**8g**	Ph	Ph	Ph	4-$CH_3C_6H_4$	*t*-Bu	82
8	**8h**	Ph	Ph	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	*t*-Bu	77
9	**8i**	Ph	Ph		4-$CH_3C_6H_4$	*t*-Bu	83
10	**8j**	Ph	Ph		4-$CH_3C_6H_4$	*t*-Bu	82
11	**8k**	Ph	4-$CH_3C_6H_4$	4-ClC_6H_4	4-$CH_3C_6H_4$	*t*-Bu	78
12	**8l**	Ph	4-FC_6H_4	4-ClC_6H_4	4-$CH_3C_6H_4$	*t*-Bu	89
13	**8m**	Ph	Ph	4-ClC_6H_4	4-$CH_3C_6H_4$	*c*-C_6H_{11}	83
14	**8n**	Ph	4-FC_6H_4	Ph	4-$CH_3C_6H_4$	*t*-Bu	85
15	**8o**	Ph	Ph	4-ClC_6H_4	3-$CH_3C_6H_4$	*t*-Bu	84
16	**8p**	Ph	Ph	2-ClC_6H_4	4-$CH_3C_6H_4$	*t*-Bu	0
17	**8q**	Ph	Ph	4-$NO_2C_6H_4$	3-$CH_3C_6H_4$	*t*-Bu	0
18	**8r**	Ph	Ph	4-ClC_6H_4	2-BrC_6H_4	*t*-Bu	0
19	**8s**	Ph	Ph	HCHO	4-$CH_3C_6H_4$	*t*-Bu	0
20	**8t**	Ph	Ph	$NH_3 \cdot H_2O$	4-$CH_3C_6H_4$	*t*-Bu	0

[a] Reaction condition: 1) MeOH, r.t., 12-24 h; 2) MeCN, Cs_2CO_3, 80 °C, 4-5 h.

[b] Isolated yields based on propenoic acids **3**

to optimize the reaction (Scheme 3). To our delight, they processed smoothly in methanol at room temperature for 12 hours, then the solvent was changed to acetonitrile and the reaction mixture was heated to reflux for 4-5 h. The reaction did not afford any product in the absence of a base or the presence of weaker bases such as NEt_3, $NaHCO_3$ (Table 1, entry 1-3). Pleasingly, a positive result encouraged us, with 1 equiv. K_2CO_3 as a base, the desired product **8a** was formed in 50% isolated yield, which increased to 70 % when K_2CO_3 was used in 3-fold excess (Table 1, entry 4 and 5). We assumed that a stronger base was probably helpful for improving reaction efficiency. Among the bases screened, it was revealed that 1 equiv. Cs_2CO_3 was the most effective base to provide cyclization products **8a** (Table 1, entry 1-8). Next, the effect of solvents was also investigated with 1 equiv. Cs_2CO_3 as a base. The screening results showed that acetonitrile was found to be the best choice. Switching to other solvents such as DMF, THF, and toluene resulted in a decreased yield (Table 1, entry 9-11).

The exact structure of compound **8a** was confirmed by NMR, HRMS, and X-ray. Furthermore, a single crystal was obtained from the MeCN/DCM solution, and the X-ray structure analysis verified the proposed structure. It is noteworthy that two double bonds all have E configuration, and five-membered ring of *γ*-lactam system adopts a planar conformation (Figure 2).

With the optimized reaction conditions in hand (Table 1, entry 6), various propenoic acids **3**, aldehydes **4**, amines **5** and isocyanides **6** were employed for the one-pot metal-free Ugi 4CR/intramolecular 5-*exo-dig* cyclization reaction. The four-

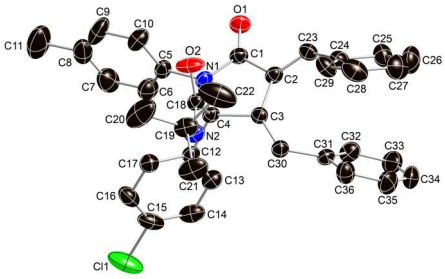
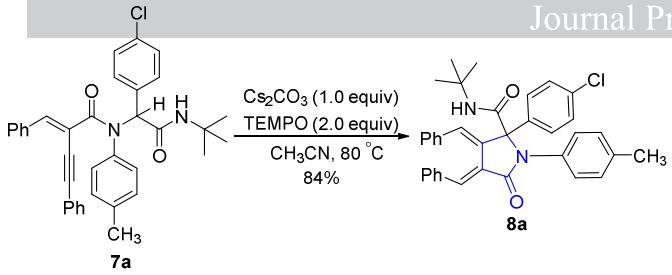


Figure 2 ORTEP drawing of compound **8a** with 50% probability thermal ellipsoids

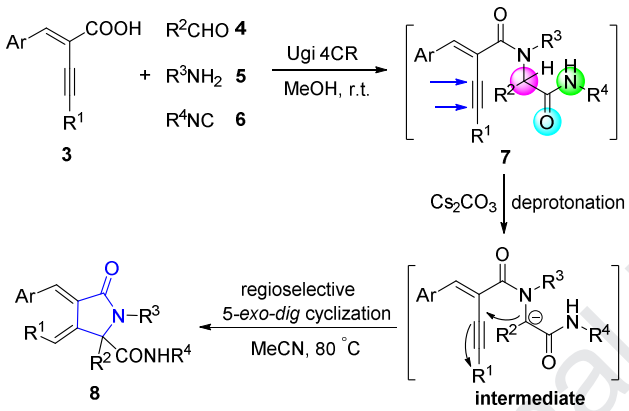
components with different substituents carried out smoothly to give the corresponding *γ*-Lactams **8** in moderate to good yields (Table 2, compounds **8a-8o**, 72-89%). In good to high yields afforded when aldehydes or acids carrying an electron-withdrawing group and amines carrying an electron-donating group were utilized (Table 2, compounds **8a**, **8f**, **8l**, **8n**, **8o**, 84%-89%). Two different heteroaryl aldehydes were also explored to get the desired products in moderate yields (Table 2, compounds **8i**, **8j**, 82%-83%). However, no products were reached when aliphatic aldehydes or amines, aromatic aldehyde with strongly electron withdrawing group (-NO_2) group, and *ortho*-substituted aromtic aldehydes or amines were used (Table 2, compounds **8p-8t**). It is noteworthy that isocyanides have little effect.

To gain an understanding of the reaction mechanism, we conducted the control experiment. As shown in Scheme 4, comparable results are observed with or without TEMPO as an



Scheme 4 Mechanism exploration

additive which showing that the reaction did not undergo a radical pathway. Based on the result presented above and previous reports[23], we postulated a plausible mechanism for the regioselective formation of these γ-Lactams (Scheme 5). Two amide moieties, a triple and a C-H bond together exist in the structure of Ugi adduct **7**. Initially, under the action of Cs_2CO_3, the C-H bond which has an acidic character could be deprotonated to form the carbanion. Subsequently, the carbanion regioselectively adds to the triple bond in Ugi adduct **7** by intramolecular nucleophilic addition to form γ-Lactams **8**.



Scheme 5. Plausible mechanism for the regioselective formation of γ-Lactams

3. Conclusion

In conclusion, we have introduced a new one-pot and regioselective preparation of functionalized γ-lactams by a metal-free Ugi 4CR/intramolecular 5-*exo-dig* cyclization reaction under mild conditions. The used propenoic acids, aldehydes, amines and isocyanides can be varied broadly and produced γ-lactams with amplified molecular complexity. Moreover, mild reaction conditions, metal-free, easy work, atomic economy and good to excellent yields all make it useful in synthetic and medicinal chemistry.

4. Experimental Section

4.1 General

General information: Reactions were generally carried out in an appropriate round bottom flask with magnetic stirring. Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. The X-ray diffraction data were collected on a Bruker APEX-II CCD equipped with 1K CCD instrument by using a graphite monochromator utilizing Mo-Kα radiation (λ=0.71073Å). HRMS (ESI) was performed on a Thermo Scientific LTQ Orbitrap XL. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 500 or 600 spectrometer and resonances were relative to TMS. Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 500/600 (125/150 MHz) with complete proton decoupling spectrophotometers ($CDCl_3$: 77.0 ppm).

*4.2 One-Pot and regioselective synthesis of functionalized γ-lactams **8***

A mixture of propenoic acids **3** (1 mmol), aldehydes **4** (1 mmol), amines **5** (1 mmol) and isocyanides **6** (1 mmol) were stirred in methanol (5 mL) at room temperature for 12-24 h, then the solvent was evaporated under reduced pressure. MeCN (5 mL) and Cs_2CO_3 (0.326 g, 1 mmol) were added to the reaction system and the reaction mixture were heated to 80 °C for 4-5 h to form γ-lactams **8**. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica ge (petroleum ether/ethyl acetate = 100 : 1, V: V) to give **8**.

*4.2.1 3,4-di((E)-benzylidene)-N-(tert-butyl)-2-(4-chlorophenyl)-5-oxo-1-(p-tolyl)pyrrolidine-2-carboxamide (**8a**)*

yellow solid (yield 476 mg, 85%). mp: 213-214 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.69 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 4H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.01-7.00 (t, *J* = 7.2 Hz, 1H), 6.93-6.77 (m, 9H), 6.67 (s, 1H), 6.10 (s, 1H), 2.29 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.7, 168.2, 136.8, 136.2, 136.1, 136.0, 134.9, 134.2, 133.9, 133.8, 130.9, 129.7, 129.5, 129.4, 129.1, 128.9, 128.5, 128.3, 128.1, 127.9, 127.1, 125.0, 124.3, 120.4, 77.4, 52.0, 28.4, 20.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{36}H_{34}ClN_2O_2$: 561.2303; found: 561.2306.

*4.2.2 3,4-di((E)-benzylidene)-N-(tert-butyl)-1,2-bis(4-chlorophenyl)-5-oxopyrrolidine-2-carboxamide (**8b**)*

yellow solid (yield 435 mg, 75%). mp: 166-167 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.69 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 9 Hz, 2H), 7.25-7.24 (t, *J* = 7.8 Hz, 4H), 7.02-7.01 (t, *J* = 7.2 Hz, 1H), 6.94-6.78 (m, 9H), 6.65 (s, 1H), 6.01 (s, 1H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6, 167.9, 136.2, 136.0, 135.9, 135.2, 134.8, 134.1, 131.5, 130.7, 129.7, 129.5, 129.3, 128.9, 128.3, 128.0, 127.2, 125.5, 124.5, 77.2, 52.2, 28.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{35}H_{31}Cl_2N_2O_2$: 581.1757; found: 581.1754.

*4.2.3 3,4-di((E)-benzylidene)-1-(4-bromophenyl)-N-(tert-butyl)-2-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxamide (**8c**)*

yellow solid (yield 449 mg, 72%). mp: 196-197 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (s, 1H), 7.53 (d, *J* = 11 Hz, 2H), 7.40 (d, *J* = 11 Hz, 2H), 7.30-7.23 (m, 4H), 7.02-7.00 (t, *J* = 9 Hz, 1H), 6.95-6.77 (m, 9H), 6.65 (s, 1H), 6.00 (s, 1H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 167.9, 136.2, 136.0, 135.9, 135.7, 134.8, 134.1, 131.8, 130.6, 129.7, 129.5, 129.3, 128.3, 128.0, 127.2, 125.7, 124.5, 119.4, 77.2, 52.2, 28.4; HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{35}H_{30}BrClKN_2O_2$: 663.0811; found: 663.0809.

*4.2.4 3-((E)-benzylidene)-N-(tert-butyl)-4-((E)-4-methylbenzylidene)-5-oxo-2-phenyl-1-(p-tolyl)pyrrolidine-2-carboxamide (**8d**)*

yellow solid (yield 453 mg, 84%). mp: 160-161 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (s, 1H), 7.55 (d, *J* = 9 Hz, 2H), 7.24-7.18 (m, 5H), 7.05-6.91 (m, 5H), 6.84-6.78 (m, 4H), 6.68 (s, 1H), 6.60 (d, *J* = 10 Hz, 2H), 6.10 (s, 1H), 2.27 (s, 3H), 2.12 (s, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 168.6, 138.2, 138.1, 135.9, 135.6, 135.2, 134.2, 133.6, 133.4, 129.7, 129.5, 129.4, 129.2, 128.9, 128.2, 127.9, 127.8, 127.0, 125.6, 124.8, 78.2, 51.9, 28.4, 21.1, 20.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{37}H_{37}N_2O_2$: 541.2850; found: 541.2845.

*4.2.5 3,4-di((E)-benzylidene)-N-(tert-butyl)-2-(4-chlorophenyl)-5-oxo-1-phenylpyrrolidine-2-carboxamide (**8e**)*

yellow solid (yield 442 mg, 81%). mp: 197-198 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (s, 1H), 7.55 (d, *J* = 11 Hz, 2H), 7.38-7.28 (m, 4H), 7.23-7.13 (m, 3H), 7.03-6.77 (m, 10H), 6.69 (s, 1H), 6.07 (s, 1H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6, 168.1, 136.7, 136.6, 136.2, 136.1, 134.9, 134.5, 133.8, 130.7, 129.4, 129.2, 128.8, 128.3, 128.1, 127.9, 127.2, 126.1, 124.9, 124.1, 77.4, 52.0, 28.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{35}H_{32}ClN_2O_2$: 547.2147; found: 547.2143.

*4.2.6 3,4-di((E)-benzylidene)-N-(tert-butyl)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (**8f**)*

yellow solid (yield 507 mg, 88%). mp: 155-156 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (s, 1H), 7.49 (d, *J* = 11 Hz, 2H), 7.22-7.19 (m, 4H), 7.02-7.00 (t, *J* = 9.25 Hz, 1H), 6.93-6.78 (m, 11H), 6.68 (s, 1H), 6.13 (s, 1H), 3.77 (s, 3H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 168.4, 157.7, 136.8, 136.3, 135.9, 135.0, 134.1, 133.9, 131.0, 130.0, 129.4, 129.1, 128.4, 128.1, 127.9, 127.2, 126.3, 125.0, 114.0, 77.7, 55.4, 52.1, 28.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{36}H_{34}ClN_2O_3$: 577.2252; found: 577.2245.

*4.2.7 3,4-di((E)-benzylidene)-N-(tert-butyl)-5-oxo-2-phenyl-1-(p-tolyl)pyrrolidine-2-carboxamide (**8g**)*

yellow solid (yield 432 mg, 82%). mp: 142-143 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 1H), 7.57-7.55 (m, 2H), 7.24-7.18 (m, 5H), 7.06-6.89 (m, 8H), 6.83-6.77 (m, 4H), 6.70 (s, 1H), 6.12 (s, 1H), 2.27 (s, 3H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 168.5, 138.1, 136.5, 136.4, 135.9, 135.1, 134.2, 133.8, 129.6, 129.5, 129.4, 129.2, 128.9, 128.3, 127.9, 127.7, 127.1, 125.4, 124.7, 78.2, 51.9, 28.4, 20.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{36}H_{35}N_2O_2$: 527.2693; found: 527.2684.

*4.2.8 3,4-di((E)-benzylidene)-N-(tert-butyl)-5-oxo-1,2-di-p-tolyl pyrrolidine-2-carboxamide (**8h**)*

yellow solid (yield 416 mg, 77%). mp: 170-171 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (s, 1H), 7.44 (d, *J* = 10 Hz, 2H), 7.21 (d, *J* = 11 Hz, 2H), 7.06-6.88 (m, 10 H), 6.83-6.76 (m, 4H), 6.68 (s, 1H), 6.08 (s, 1H), 2.27 (d, *J* = 6.5 Hz, 6H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 168.6, 137.6, 136.6, 135.8, 135.2, 135.0, 134.3, 133.7, 129.4, 129.2, 128.9, 128.6, 128.3, 127.6, 127.1, 125.6, 124.8, 78.2, 51.9, 28.4, 21.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{37}H_{37}N_2O_2$: 541.2850; found: 541.2842.

*4.2.9 3,4-di((E)-benzylidene)-N-(tert-butyl)-2-(furan-2-yl)-5-oxo -1-(p-tolyl)pyrrolidine-2-carboxa-mide (**8i**)*

yellow solid (yield 428 mg, 83%). mp: 203-204 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (s, 1H), 7.19 (d, *J* = 10.5 Hz, 2H), 7.11 (d, *J* = 10.5 Hz, 2H), 7.03-6.76 (m, 12H), 6.70 (s, 1H), 6.29-6.28 (m, 1H), 6.10 (s, 1H), 2.31 (s, 3H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.7, 167.2, 149.9, 142.7, 136.4, 136.3, 135.3, 133.9, 133.8, 132.4, 129.4, 129.3, 129.2, 128.9, 128.4, 127.7, 127.1, 125.0, 124.6, 113.3, 110.3, 74.1, 51.9, 28.4, 21.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{34}H_{33}N_2O_3$: 517.2486; found: 517.2489.

*4.2.10 3,4-di((E)-benzylidene)-N-(tert-butyl)-5-oxo-2-(thiophen-2-yl)-1-(p-tolyl)pyrrolidine-2-carboxamide (**8j**)*

yellow solid (yield 436 mg, 82%). mp: 172-173 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (s, 1H), 7.33 (d, *J* = 10.5 Hz, 3H), 7.10 (d, *J* = 10.5 Hz, 2H), 7.03-6.75 (m, 13H), 5.98 (s, 1H), 2.30 (s, 3H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.4, 168.4, 140.9, 136.2, 135.9, 135.5, 135.1, 134.5, 134.1, 129.4, 129.3, 129.0, 128.6, 128.4, 127.8, 127.7, 127.4, 127.1, 126.0, 124.7, 123.7, 75.1, 52.0, 28.3, 20.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{34}H_{33}N_2O_2S$: 533.2257; found: 533.2257.

*4.2.11 3-((E)-benzylidene)-N-(tert-butyl)-2-(4-chlorophenyl)-4-((E)-4-methylbenzylidene)-5-oxo-1-(p-tolyl)pyrrolidine-2-carboxamide (**8k**)*

yellow solid (yield 448 mg, 78%). mp: 190-191 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 1H), 7.52 (d, *J* = 10.5 Hz, 2H), 7.20 (d, *J* = 11 Hz, 4H), 7.07 (d, *J* = 10.5 Hz, 2H), 7.00-6.97 (m, 1H), 6.91-6.76 (m, 6H), 6.65-6.59 (m, 3H), 6.09 (s, 1H), 2.28 (s, 3H), 2.13 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 168.4, 138.3, 136.9, 136.1, 135.2, 135.0, 134.0, 133.7, 133.4, 130.9, 129.8, 129.6, 129.4, 129.1, 129.0, 128.5, 128.3, 128.0, 127.8, 127.1, 125.2, 124.3, 120.3, 77.4, 52.0, 29.4, 28.4, 21.1, 20.9; HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{37}H_{35}ClKN_2O_2$: 613.2019; found: 613.2023.

*4.2.12 3-((E)-benzylidene)-N-(tert-butyl)-2-(4-chlorophenyl)-4-((E)-4-fluorobenzylidene)-5-oxo-1-(p-tolyl)pyrrolidine-2-carboxamide (**8l**)*

yellow solid (yield 515 mg, 89%). mp: 177-178 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (s, 1H), 7.52 (d, *J* = 11 Hz, 2H), 7.22-7.18 (m, 4H), 7.08-7.05 (m, 3H), 6.93-6.84 (m, 6H), 6.61 (s, 1H), 6.50-6.48 (t, *J* = 10.75 Hz, 2H), 6.13 (s, 1H), 2.29 (s, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 168.2, 163.7, 161.2, 136.8, 136.1, 135.9, 134.9, 134.1, 133.8, 132.3, 130.9, 130.1, 130.0, 129.5, 129.4, 128.7, 128.1, 127.3, 125.0, 124.3, 114.3, 114.0, 77.4, 52.1, 28.4, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.694; HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{36}H_{32}ClFKN_2O_2$: 617.1768; found: 617.1758.

*4.2.13 3,4-di((E)-benzylidene)-2-(4-chlorophenyl)-N-cyclohexyl-5-oxo-1-(p-tolyl)pyrrolidine-2-carboxamide (**8m**)*

yellow solid (yield 487 mg, 83%). mp: 233-234 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (s, 1H), 7.53 (d, *J* = 11 Hz, 2H), 7.19-7.16 (m, 4H), 7.05-6.75 (m, 12H, Ar-H), 6.68 (s, 1H), 6.27 (d, *J* = 10.5 Hz, 1H), 3.94-3.84 (m, 1H), 2.27 (s, 3H), 1.85-0.91 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 168.3, 137.0, 136.3, 136.2, 135.7, 135.0, 134.2, 133.8, 131.1, 130.6, 129.4, 129.1, 128.4, 128.1, 127.8, 127.1, 124.9, 124.6, 77.2, 49.0, 32.7, 32.6, 25.2, 24.7, 24.6, 20.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{38}H_{36}ClN_2O_2$: 587.2460; found: 587.2452.

*4.2.14 3-((E)-benzylidene)-N-(tert-butyl)-4-((E)-4-fluorobenzylidene)-5-oxo-2-phenyl-1-(p-tolyl)pyrrolidine-2-carboxamide (**8n**)*

yellow solid (Yield 463 mg, 85%). mp: 175-176 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (s, 1H), 7.56-7.54 (m, 2H), 7.25-7.16 (m, 5H), 7.04 (d, *J* = 10 Hz, 3H), 6.95-6.85 (m, 6 H), 6.65 (s, 1H), 6.50-6.47 (t, *J* = 10.75 Hz, 2H), 6.14 (s, 1H), 2.27 (s, 3H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.7, 168.5, 163.5, 161.1, 138.1, 136.2, 136.0, 135.0, 134.1, 133.7, 132.5, 130.0, 129.9, 129.5, 129.4, 129.3, 128.5, 127.9, 127.2, 125.4, 124.7, 78.2, 52.0, 28.4, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.079; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{36}H_{34}FN_2O_2$: 545.2599; found: 545.2601.

*4.2.15 3,4-di((E)-benzylidene)-N-(tert-butyl)-1-(4-chlorophenyl)-5-oxo-2-(m-tolyl)pyrrolidine-2-carboxamide (**8o**)*

yellow solid (yield 471 mg, 84%). mp: 169-170 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.69 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.22-7.21 (m, 3H), 7.15-7.14 (t, *J* = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.02-6.89 (m, 7H), 6.83-6.78 (m, 4H), 6.69 (s, 1H), 6.08 (s, 1H), 2.28 (s, 3H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.7, 168.1, 138.7, 136.8, 136.5, 136.2, 136.1, 134.9, 134.3, 133.8, 130.8, 129.5, 129.4, 129.1, 128.6, 128.3, 128.0, 127.9,

127.2, 127.0, 125.0, 121.2, 77.4, 52.0, 28.3, 21.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{36}H_{34}ClN_2O_2$: 561.2303; found: 561.2307.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at.

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Highlights

- We provided a new one-pot and regioselective synthesis of functionalized γ-lactams by a metal-free Ugi 4CR/intramolecular 5-*exo*-*dig* cyclization sequence.
- There is no report previously on the sequential Ugi 4CR/intramolecular cyclization to prepare *γ*-lactams regioselectively by using propenoic acid as acid component in the Ugi reaction.
- Owing to the high atom efficiency, the good yields, the mild reaction conditions, metal-free and the easily available starting materials, the efficient synthesis will make it useful in synthetic and medicinal chemistry.

Deciaration of Interest State

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest.

We confirm that the manuscript has been read and agreed by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and there are no impediments to publication, including the timing of publication with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectural property.

We understand that the corresponding author is the sole contact for the Editorial process. She is responsible for communicating with other authors about the progress, submission of revision and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the corresponding author and which has been confirmed to accept email from ***Tetrahedron.***

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