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Synthesis of α,β-Unsaturated 2-Oxopyrrolidinyl Acetamide Derivatives by Application of the Ugi/RCM Reaction Sequence†

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The Ugi four-component condensation reaction have been widely used for the construction of focused library and diversity-oriented approach especially in the drug discovery, and also applied to introduce more complexity by utilizing bifunctional components or post transformations.[1]

The various constructions of γ-lactam ring based on the Ugi reaction have been reported. The preparations were successfully accomplished by using γ-ketoacids as bifunctional starting materials[2] or post transformation strategies such as Horner-Wadsworth-Emmons reaction,[3] Heck reaction,[4] cyclization,[5] deBoc-Cyclization,[6] and radical cyclization[7] from appropriate starting materials. It was also found that bicyclic γ-lactam moiety can be accessed by a tandem Ugi/Diels–Alder reaction followed by domino metathesis.[8] The sequential Ugi reaction/ring-closing metathesis (RCM) reaction provided powerful synthetic tools toward macrocyclic lactams larger than five-membered 2-pyrrolidones.[9]

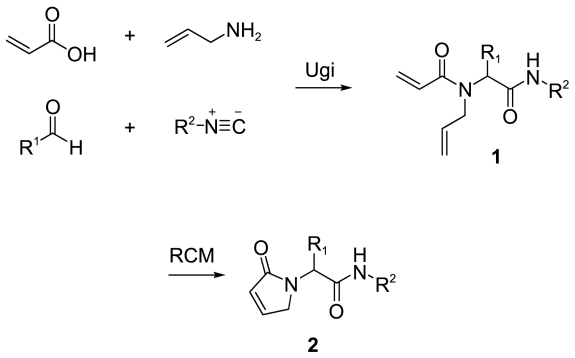
As an extension of our work with the Ugi reaction,[10] we became interested in the Ugi/RCM reaction protocol to expand the scope of scaffold generated by this versatile reaction. Herein, we report the construction of α,β-unsaturated piracetam derivatives, an important synthon to diversify piracetam scaffolds in the drug discovery.[11]

The 2-pyrrolidinone family of cognition enhancers, exampplified by piracetam analogues, 2-oxo-1-pyrrolidineacetamides, are of interest due to their biological activities such as nootropics, cognition enhancing, antidementia, anticholinergic, antiepileptics, antihistaminic, antidepressants, anxiety, and hypoxia with a lack of clear mechanism of action (Figure 1).[12]

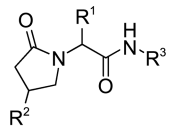
Moreover Levetiracetam (Keppra®, 2000, UCB),[13] the α-ethyl analogue of the nootropic piracetam, is a second-generation antiepileptic drug in the oral treatment of partial-onset seizures. Its mechanism of action appears to involve binding to synaptic vesicle protein 2A and blocking N-type calcium channel.

As shown in Scheme 1, an Ugi four-component coupling followed by ring-closing metathesis reaction was envisaged to provide α,β-unsaturated γ-lactam **2**. The lactam scaffolds **2** are able to be constructed by a sequential ring closing metathesis (RCM) reaction of the Ugi adduct **1**, which can be readily prepared by using acrylic acid, allylamine, various aldehydes and isocyanides.

At first, the Ugi reaction of acrylic acid with allylamine, formaldehyde and *tert*-butylisocyanide was proceeded in 2,2,2-trifluoroethanol at 0 °C, and the mixture was stirred for 24 h at room temperature to afford acrylamide **1d** in 52% yield (Table 1, entry 4). The reaction of the acrylic acid and allylamine with various isocyanides and formaldehyde or



Scheme 1. A sequential Ugi/RCM reaction to α,β-unsaturated piracetam analogues.

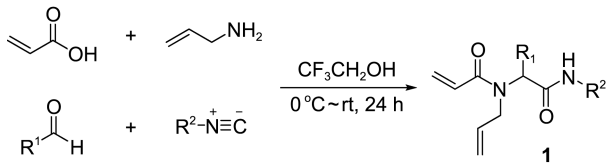


	R^1, R^2, R^3 =
Piracetam:	H, H, H (1972, 1999, UCB)
Oxiracetam:	H, OH, H (1987, GSK)
Pramiracetam:	H, OH, $(i\text{Pr})_2NCH_2CH_2$- (1993, Frima)
Levetiracetam:	Ethyl (*S*), H, H (2000, UCB)
Brivaracetam:	Ethyl (*S*), Propyl, H (III)
Seletracetam:	Ethyl (*S*), F_2CCH-, H (II)
Nefiracetam:	H, H, 2,6-dimethylphenyl (II)
Coluracetam:	H, H, 2-3-dimethyl-tetrahydrofuro[2,3-*b*]quinolin-4-yl (II)

Figure 1. The chemical structures of piracetam-related drugs.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

Table 1. Preparation of acrylamide **1** by Ugi four-component reaction of acrylic acid[a]



1

Entry	R^1	R^2	Product	Yield (%)[b]
1	H	4-methoxybenzyl	**1a**	65
2	H	benzyl	**1b**	62
3	H	2,4-dimethoxybenzyl	**1c**	32
4	H	*tert*-butyl	**1d**	52
5	C_2H_5-	benzyl	**1e**	46
6	C_2H_5-	4-methoxybenzyl	**1f**	65
7	C_2H_5-	2,4-dimethoxybenzyl	**1g**	30

[a]All reactions were carried out with allylamine (1.0 equiv), acrylic acid (1.0 equiv), aldehyde (1.0 equiv) and an isocyanide (1.2 equiv) in 2,2,2-trifluoroethanol at room temperature for 24 h. [b]Isolated yield.

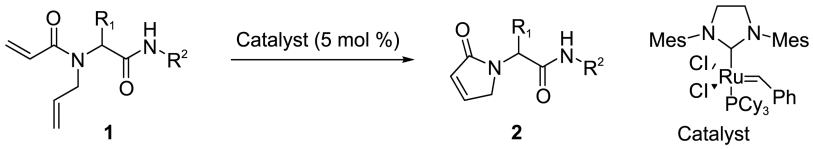
propionaldehyde provided α,β-unsaturated amide **1** in moderate to good yields (Table 1). The required isocyanides were purchased or prepared from the corresponding formamides by treating them with triphosgene following the reported methods.[14]

Ring-closing metathesis reaction of acrylamides **1** provided the five-membered α,β-unsaturated γ-lactam **2** in 51-76% yield (Table 2). All reactions were conducted either in benzene or toluene at 80 °C condition in the presence of 2-5 mol % of Grubbs second generation ruthenium catalyst for 4 h. Initial experiments with the Grubbs first-generation catalyst were unsuccessful with very little conversion despite elevated catalyst loading and prolonged reaction time. The reaction in dichloromethane under reflux condition was not proceeded in the presence of both Grubbs first and second generation catalyst (entry 1). The optimum procedure of RCM reaction was found that a solution of the Grubbs second generation catalyst (5 mol %) was added slowly with syringe pump during 2 h to a highly diluted solution of the Ugi adducts **1** in toluene (0.03 M) at 80 °C and further stirring for 2 h at the same temperature. Pyrrolidone butanamides (**2e-g**), a synthetic precursor of racemic levetiracetam, were also obtained in good yields. Further hydrogenation of γ-lactam **2e** with 10% Pd/C catalyst under hydrogen gas gave the corresponding saturated γ-lactam in 80% yield.

We next turned our attention to examining the scope of ring-closing enyne metathesis. The Ugi reaction of propargyl amine with acrylic acid, formaldehyde and benzylisocyanide gave a acrylamide **3** in 45% yield, and the subsequent enyne metathesis under the previous RCM reaction condition gave the diene **4** in 24% yield (Scheme 2).

Furthermore, the reaction of propiolic acid with allylamine, formaldehyde, and benzyl isocyanide provided propiolamide **5** in 77% yield by a typical Ugi four-component reaction. The results of following enyne metathesis reaction of the Ugi adduct **5** were shown in Table 3. When the reaction was carried out under refluxing benzene or toluene at 80 °C con-

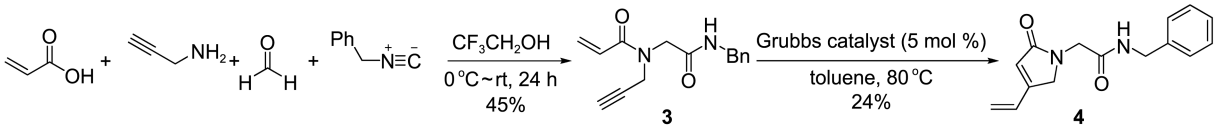
Table 2. Synthesis of α,β-unsaturated γ-lactam **2** by ring-closing metathesis reaction with grubbs second generation catalyst[a]



1 **2** Catalyst

Entry	R^1	R^2	Solvent	Product	Temp.	Yield (%)[b]
1	H	4-methoxybenzyl	DCM	**2a**	reflux	NR
2	H	4-methoxybenzyl	benzene	**2a**	reflux	Trace
3	H	4-methoxybenzyl	toluene	**2a**	80 °C	63
4	H	benzyl	toluene	**2b**	80 °C	50
5	H	2,4-dimethoxybenzyl	toluene	**2c**	80 °C	64
6	H	*tert*-butyl	toluene	**2d**	80 °C	51
7	C_2H_5-	benzyl	benzene	**2e**	reflux	76
8	C_2H_5-	benzyl	toluene	**2e**	80 °C	60
9	C_2H_5-	4-methoxybenzyl	toluene	**2f**	80 °C	66
10	C_2H_5-	2,4-dimethoxybenzyl	toluene	**2g**	80 °C	61

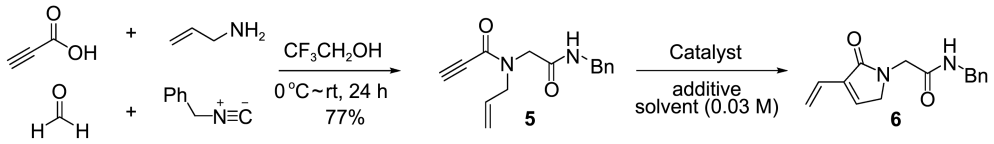
[a]All reactions were carried out with unsaturated amide with 5 mol % of Grubbs second generation catalyst under highly diluted condition (0.03 M) at reflux or 80 °C for 4 h. [b]Isolated yield.



3 **4**

Scheme 2. A tandem Ugi and Ring-closing enyne metathesis sequence from propargyl amine.

Table 3. An Ugi reaction of propiolic acid and subsequent enyne metathesis reaction[a]



Entry	Grubbs' Cat.	Additive	Solvent	Yield[b]
1	5.0 mol %	–	DCM, reflux	NR
2	5.0 mol %	–	Benzene, reflux	30%
3	5.0 mol %	–	Toluene, 80 °C	41%
4	5.0 mol %	Ti(O*i*-Pr)$_4$ (0.3eq)	DCM, reflux	25%
5	10.0 mol %	Ti(O*i*-Pr)$_4$ (0.3eq)	DCM, reflux	41%
6	5.0 mol %	Ti(O*i*-Pr)$_4$ (1.0eq)	DCM, reflux	28%
7	5.0 mol %	Ti(O*i*-Pr)$_4$ (2.0eq)	DCM, reflux	64%

[a]All reactions were carried out with propiolamide with 5 mol % of Grubbs second generation catalyst under highly diluted condition (0.03 M) at reflux or 80 °C for 4 h. [b]Isolated yield.

dition, the desired product **6** was obtained in 30% and 41% yield respectively (Entry 2, 3). The RCM reaction did not proceed when dichloromethane was used as solvent under reflux condition. However, treatment of the substrate with titanium isopropoxide as co-catalyst (0.3 equiv) in refluxing dichloromethane, which was reported to destabilize complex between the ruthenium catalyst and various hydrogen bond acceptors,[15] resulted in the formation of the expected unsaturated γ-lactam **6** in 25% yield (Entry 4). Increasing the used amount of the Grubbs catalyst or titanium isopropoxide gave higher yields (Entry 5, 6). Finally, the reaction of propiolamide **5** with the 5 mol % Grubbs second generation catalyst in the presence of 2 equiv of titanium isopropoxide in dichloromethane (40 °C) for 4 h afforded the lactam **6** in 64% yield.

In conclusion, we have developed an Ugi/RCM reaction sequence for the convenient synthesis of α,β-unsaturated γ-lactams derivatives. The Ugi reaction with appropriate combinations of each component and a subsequent ring-closing olefin or enyne metathesis reaction as a post-condensation transformation gave α,β-unsaturated pyrrolidone acetamide derivatives, nootropic piracetam analogues, in an efficient method. Further chemical transformations of the lactams, and the biological activities of the prepared piracetam derivatives are under study.

Experimental Section

A General Procedure for the Ugi Reaction. The solution of acrylic acid or propiolic aid (0.4 mmol) and an isocyanide (0.48 mmol) in 2,2,2-trifluoroethanol (4 mL) was added slowly to a suspension of allylamine or propargylamine (0.4 mmol), and formaldehyde in 2,2,2-trifluoroethanol (10 mL) at 0 °C under nitrogen. The mixture was allowed to reach room temperature. After stirring for 24 h, the reaction mixture was concentrated under reduced pressure. Water (10 mL) and EtOAc (20 mL) were added to the residue, and the resulting aqueous solution was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 1:1 or 1:2 mixture of hexane and ethyl acetate as an eluent.

***N*-Allyl-*N*-[(4-methoxy-benzylcarbamoyl)methyl]-acrylamide (1a):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 2H, J = 9.0 Hz), 6.95 (br. t, 1H), 6.84 (d, 2H, J = 9.0 Hz), 6.53-6.44 (m, 1H), 6.36-6.30 (m, 1H), 5.82-5.75 (m, 1H), 5.74-5.70 (m, 1H), 5.24-5.12 (m, 2H), 4.34 (d, 2H, J = 6.0 Hz), 4.09 (d, 2H, J = 6.0 Hz), 4.02 (s, 2H), 3.77 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.84, 167.47, 158.84, 131.97, 130.21, 129.75, 128.90, 126.81, 117.47, 113.96, 55.25, 51.42, 50.69, 42.77; HRMS (EI) calcd for $C_{16}H_{20}N_2O_3$ (M^++H) 288.1474, found 288.1474.

***N*-Allyl-*N*-(benzylcarbamoylmethyl)acrylamide (1b):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.18-7.05 (m, 5H, aromatic), 6.34-6.31 (m, 1H), 6.21-6.16 (m, 1H), 5.61-5.55 (m, 2H), 5.11-4.99 (m, 2H), 4.26 (d, 2H, J = 3.0 Hz), 3.96 (d, 2H, J = 6.0 Hz), 3.91 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.94, 167.44, 138.20, 132.08, 129.29, 128.56, 127.47, 127.25, 126.91, 117.40, 51.43, 50.47, 43.21; HRMS (EI) calcd for $C_{15}H_{18}N_2O_2$ (M^++H) 258.1368, found 258.1361.

***N*-(*tert*-Butyl)-2-[(*N*-allyl-*N*-propenoyl)amino]acetamide (1d):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.57-6.36 (m, 2H), 5.87-5.73 (m, 2H), 5.26-5.15 (m, 2H), 4.10(br. s, 1H), 3.93 (s, 2H), 1.32 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.15, 167.26, 133.99, 132.08, 129.13, 126.98, 117.35, 51.68, 51.35, 51.09, 28.61; HRMS (EI) calcd for $C_{12}H_{20}N_2O_2$ (M^++H) 224.1525, found 224.1524.

***N*-(4-Methoxybenzyl)-2-[(*N*-allyl-*N*-propenoyl)amino]butanamide (1f):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15-7.12 (d, 2H, J = 9.0 Hz), 6.84-6.81 (d, 3H, J = 9.0 Hz), 6.53-6.33 (m, 2H), 6.81-5.70 (m, 2H), 5.18-5.12 (m, 2H), 4.88 (t, 1H, J = 9.0Hz), 4.40-4.24 (d, 2H, J = 6.0 Hz), 4.12-3.91 (d, 2H, J = 6.0 Hz), 3.78 (s, 3H), 2.03 (m, 1H), 1.67 (m, 1H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.34, 168.01, 158.83, 134.25, 130.32, 129.31, 128.90, 127.94,

116.94, 113.95, 58.84, 55.28, 46.79, 42.75, 21.41, 10.82; HRMS (EI) calcd for $C_{18}H_{24}N_2O_3$ (M^++H) 316.1787, found 316.1785.

A General Procedure for the RCM. A homogeneous orange-red solution of Grubbs 2nd catalyst (9.3 mg, 0.01 mmol) was added slowly with syringe pump to the diene or enyne (0.50 mmol) in 15 mL of dry toluene under argon at 80 °C for 2 h. The resulting mixture was stirred for 2 h at the same temperature, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by exposure to air (until greenish-black; 6 h), concentrated, and purified by flash column chromatography (0-6% Et_2O/ hexane).

***N*-(4-Methoxybenzyl)-2-(2-oxo-2,5-dihydropyrrol-1-yl) acetamide (2a):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 2H, *J* = 8.4 Hz), 7.12 (m, 1H), 6.84 (d, 3H, *J* = 8.5 Hz), 6.15 (d, 1H, *J* = 6.0 Hz), 4.34 (d, 2H, *J* = 5.6 Hz), 4.15 (br. t, 2H), 4.09 (s, 2H), 3.77 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.00, 168.24, 158.97, 144.24, 129.99, 129.02, 127.31, 114.05, 55.27, 24.13, 46.38, 42.94; HRMS (EI) calcd for $C_{14}H_{16}N_2O_3$ (M^++H) 260.1161, found 260.1167.

***N*-Benzyl-2-(2-oxo-2,5-dihydropyrrol-1-yl)acetamide (2b):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 7.14-7.12 (d, 1H, *J* = 6.0 Hz), 6.94 (br. s, 1H), 6.14 (d, 1H, *J* = 5.9 Hz), 4.40 (d, 2H, *J* = 5.7 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.06, 168.40, 168.84, 167.47, 158.84, 131.97, 130.21, 129.75, 128.90, 126.81, 117.47, 113.96, 55.25, 51.42, 50.69, 42.77; HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$ (M^++H) 230.1055, found 230.1058.

***N*-(*tert*-Butyl)-2-(2-oxo-2,5-dihydropyrrol-1-yl)acetamide (2d):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.18 (dt, 1H, *J* = 1.7, 6.0 Hz), 6.21 (dt, 1H, *J* = 1.7, 6.0 Hz), 6.02 (br. s, 1H), 4.18 (d, 2H, *J* = 1.6 Hz), 3.99 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.90, 167.58, 144.08, 127.45, 54.05, 51.45, 47.39, 28.67; HRMS (EI) calcd for $C_{10}H_{16}N_2O_2$ (M^++H) 196.1212, found 196.1205.

***N*-(4-Methoxybenzyl)-2-(2-oxo-2,5-dihydropyrrol-1-yl) butanamide (2f):** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (d, 3H, *J* = 8.7 Hz), 6.82 (d, 3H, *J* = 8.7 Hz), 6.11 (dt, 1H, *J* = 1.8, 6.0 Hz), 4.53 (t, 1H, *J* = 7.9 Hz), 4.41-4.34 (m, 1H), 4.29-4.19 (m, 2H), 4.05-3.97 (m, 1H), 3.78 (s, 3H), 2.08-1.99 (m, 1H), 1.81-1.71 (m, 1H), 0.89 (t, 3H, *J* = 4.7 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.99, 170.12, 158.89, 144.15, 130.11, 128.91, 127.22, 114.00, 56.50, 55.27, 50.32, 42.85, 22.72, 10.62; HRMS (EI) calcd for $C_{16}H_{20}N_2O_3$ (M^++H) 288.1474, found 288.1468.

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