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NOVEL RING TRANSFORMATION OF URACILS TO 2-OXAZOLIDINONES

Yoshiaki Kitamura,[1]* Yuki Nagaya,[2] Yuto Ohshima,[1] Daiki Kato,[1] Asuki Ohguchi,[1] Hiroshi Katagiri,[3] Masato Ikeda,[1,2,4] and Yukio Kitade[1,5]

[1] Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan. E-mail address: kitamura@gifu-u.ac.jp (Y. Kitamura)

[2] United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

[3] Graduate School of Science and Engineering, Yamagata University, 4-3-16 Jonan, Yonezawa, Yamagata 992-8510, Japan

[4] Gifu Center for Highly Advanced Integration of Nanosciences and Life Sciences (G-CHAIN), Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

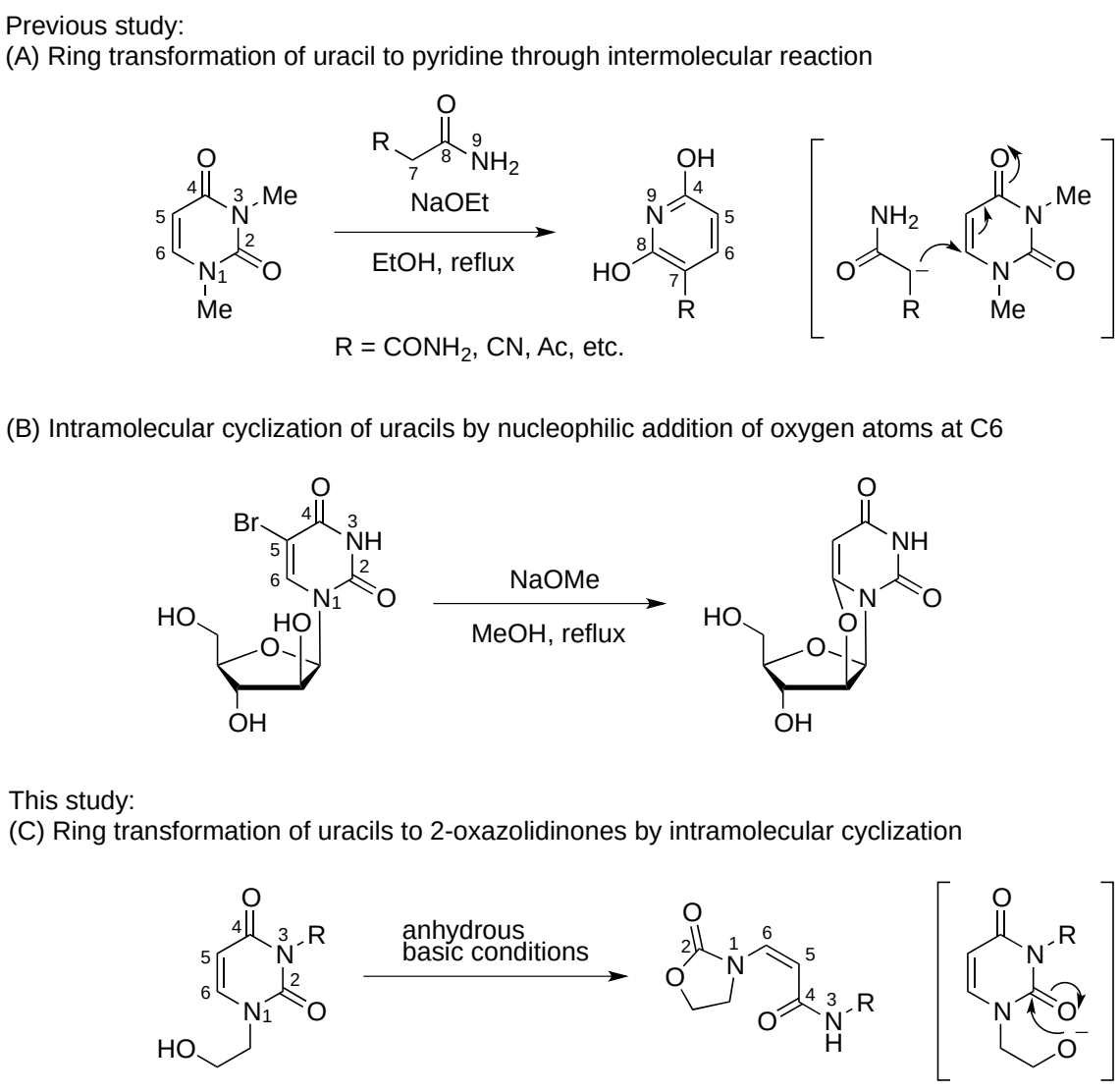
[5] Department of Applied Chemistry, Faculty of Engineering, Aichi Institute of Technology, 1247 Yachigusa, Yakusa-cho, Toyota, Aichi 470-0392, Japan

Abstract – Treatment of N^3-electron-withdrawing group-protected uracil derivatives bearing a 2-hydroxyethyl moiety at the 1-position with base under anhydrous conditions affords the corresponding 2-oxazolidinone by opening the pyrimidine ring between C2 and N3, followed by ring closure between C2 and the neighbouring hydroxy group. This ring transformation is applicable to various uracil analogues to obtain the desired 2-oxazolidinone in moderate to excellent yield.

INTRODUCTION

Uracil is one of the four nucleobases comprising RNA and its reactivity has been widely studied. Uracil derivatives can be transformed to other heterocyclic ring systems by reaction with various nucleophiles.[1] For example, uracil reacts with hydrazine and hydroxylamine to provide the corresponding pyrazolone and isoxazolone, respectively.[2] Treatment of 5-bromo-6-methyluracil derivatives bearing a phenyl group at the 1-position with methylamine gives the corresponding hydantoin.[3] Reaction of pseudouridine with methylguanidine affords N^2-methylpseudoisocytidine, which is difficult to synthesize by other methods.[4]

UV irradiation of 5-substituted 6-azido-1,3-dimethyluracils in the presence of alkylamines or alcohols furnishes the corresponding 2-alkylamino- or 2-alkoxy-1,3,5-triazepine.[5] Certain uracil derivatives react with 1,3-ambident nucleophiles such as malonamide and malononitrile in ethanolic sodium ethoxide for conversion into pyridine ring systems through nucleophilic attack by the nucleophile's carbanion on C6 of the pyrimidine ring (Scheme 1A).[6] In addition, intramolecular nucleophilic addition to uracil derivatives has been reported by several researchers.[7] For example, treatment of 5-bromo-1-(β-D-arabinofuranosyl)uracil with sodium methoxide in refluxing methanol afforded 6,2′-*O*-cyclouridine by nucleophilic attack of the 2′-oxy anion on the 6-position of the pyrimidine ring, followed by debromination (Scheme 1B).[7a]



Scheme 1. Ring transformation of uracil to other heterocyclic ring systems, and the intramolecular cyclization of uracil

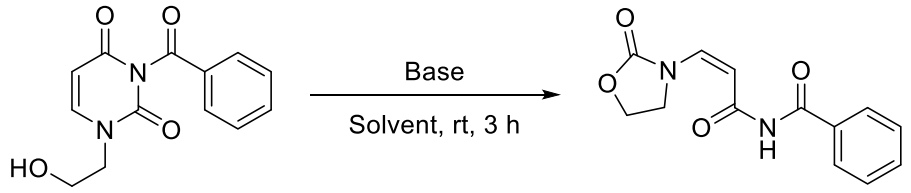
Under similar reaction conditions, 5-iodo-2′,3′-*O*-isopropylideneuridine undergoes intramolecular cyclization between C6 and the 5′-hydroxy group of the sugar moiety, followed by elimination of the iodine atom to give 2′,3′-*O*-isopropylidene-O^6,5′-cyclouridine.[7b] Treatment of 5′-azido-5-bromo-5′-deoxy-2′,3′-*O*-isopropylideneuridine with triphenylphosphine and ammonium hydroxide gave 6-amino-5′,6-*N*-anhydrouridine.[7l] Upon heating 5′-azido-5-bromo-5′-deoxy-2′,3′-*O*-isopropylideneuridine in DMF at 110-120 ºC, [2,3]-dipolar addition of the 5′-azido group to the 5,6-double bond and concomitant elimination of HBr from the adduct afforded 9,5′-cyclo-8-azaxanthosine.[7m] Many other intramolecular reactions involving the participation of atoms on the pyrimidine ring have been reported, but most involve the nucleophilic addition of oxygen and nitrogen atoms at the 6-position of 5-bromo- or 5-iodo-substituted uracil.

Our studies on the synthesis of uracil derivatives bearing a functional linker at N1 using N^1-(2-hydroxyethyl)-N^3-benzoyluracil (**1a**) under anhydrous basic conditions identified a novel uracil ring transformation to 2-oxazolidinone. This transformation involves opening the pyrimidine ring between C2 and N3 and neighbouring-group participation of the hydroxy group (Scheme 1C). The formation of 2-oxazolidinone derivatives was unambiguously determined by single-crystal X-ray diffraction analysis.[8] The reaction of **1a** with 1.0 equiv of sodium hydride (NaH) in DMSO at room temperature causes ring-opening of the uracil skeleton to afford the corresponding 2-oxazolidinone derivative **2a** in 80% yield. Here, we further advance this ring transformation to investigate the optimal reaction conditions and explore the scope and limitations of substrates.

RESULTS AND DISCUSSION

Initially, we examined the effect of solvent using **1a** as substrate in the presence of NaH (Table 1, entries 1–6). The use of DMA or DMF as solvent gave **2a** in moderate yield, whereas the use of THF, NMP or DMI gave only low yields. Notably, the present ring transformation proceeded with high efficiency in DMSO, the best solvent for the reaction. Next, we focused on the effect of bases (Table 1, entries 6–11) and found that KO^{t}Bu gave the best result of the bases studied. Although ring transformation proceeded with NaOH to afford **2a**, the yield was moderate. Weak bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and K_2CO_3 were not effective in the reaction. Therefore, a KO^{t}Bu–DMSO system was chosen as the optimized conditions.

Table 1. Effect of bases and solvents on the ring transformation reaction



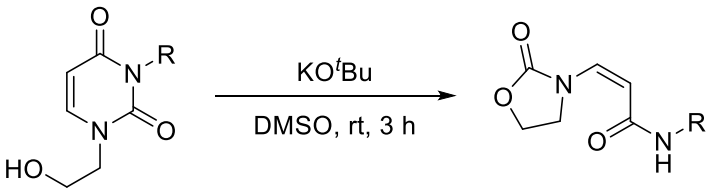
1a **2a**

Entry	Base	Solvent	Yield (%)[a]
1	NaH	THF	2
2	NaH	NMP	16
3	NaH	DMI	18
4	NaH	DMA	42
5	NaH	DMF	52
6	NaH	DMSO	84 (80)[b]
7	DABCO	DMSO	<1
8	DBU	DMSO	<1
9	K_2CO_3	DMSO	<1
10	NaOH	DMSO	53
11	KO^{t}Bu	DMSO	97 (90)[b]

[a] Determined by ^{1}H NMR (mesitylene was used as an internal standard). [b] Isolated yield.

We next explored the scope and limitations of substrates for the ring transformation of uracils to 2-oxazolidinones under the optimized conditions using various uracil derivatives (Tables 2 and 3). First, the effect of substituents at the 3-position of the uracil ring was examined (Table 2). The ring transformation of uracils to 2-oxazolidinones did not proceed with N^3-non- (**1b**), N^3-methyl- (**1c**), and N^3-phenyl- (**1d**) substituted uracils (Table 2, entries 1–3), whereas uracil derivatives bearing an electron-withdrawing group (EWG), such as the 2,4-dinitrophenyl (**1e**), *tert*-butoxycarbonyl (**1f**) and pivaloyl (**1g**) groups, provided the corresponding 2-oxazolidinone, although these EWGs were less effective than a benzoyl group (Table 2, entries 4–6 vs. entry 7). These results suggest that EWG substituents at the 3-position of the uracil ring are essential for the present ring transformation.

Table 2. Ring transformation for a series of N^3-substituted uracil analogues to 2-oxazolidinone derivatives

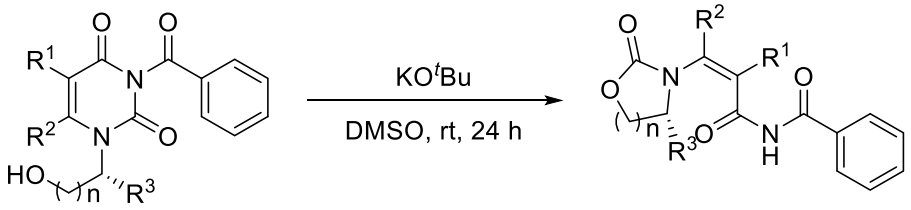


1a-1g **2a-2g**

Entry	Substrate	R	Product	Isolated yield (%)
1	**1b**	H	**2b**	0
2	**1c**	Me	**2c**	0
3	**1d**	Ph	**2d**	0
4	**1e**	2,4-$(NO_2)_2$Ph	**2e**	62
5	**1f**	Boc	**2f**	55
6	**1g**	Piv	**2g**	48
7	**1a**	Bz	**2a**	90

The application of the present method to a series of N^3-benzoyluracil derivatives is shown in Table 3. Various N^3-benzoyluracil derivatives with a substituent at the 5-position afforded the corresponding 2-oxazolidinone in moderate to high yield (Table 3, entries 2–4). Completion of the reaction with 5-fluoro analogue (**1i**) took longer than with non-substituted substrate (**1a**). In addition, the ring transformation of methyl-substituted (**1h**) and bromo-substituted (**1j**) uracils was incomplete even after 24 h. These results suggest that substituent size at the 5-position greatly affects reactivity. The desired ring transformation did not proceed with the 6-methyluracil analogue (**1k**) (Table 3, entry 5). Heating the reaction mixture resulted in removal of the N^3-benzoyl group and *O*-benzoylation of the hydroxy group. The ring transformation of uracil did not proceed with N^3-benzoyluracil derivatives with a methylene (**1l**[9]), propylene (**1m**) or butylene (**1n**) linker between N1 and the hydroxy group (Table 3, entries 6–8). In contrast, substitution on the hydroxyethyl moiety did not affect the progress of the reaction (Table 3, entries 9 and 10). The ring transformations of **1o** and **1p**, which have a chiral centre in the hydroxyethyl moiety, afforded the corresponding 2-oxazolidinones bearing an enantiomeric 4-substituted 2-oxazolidinone, which is a known chiral auxiliary, in excellent yield. In addition, no *cis-trans* epimerization was observed at all in these transformations.

Table 3. Ring transformation for a series of N^3-benzoyluracil analogues to 2-oxazolidinone derivatives



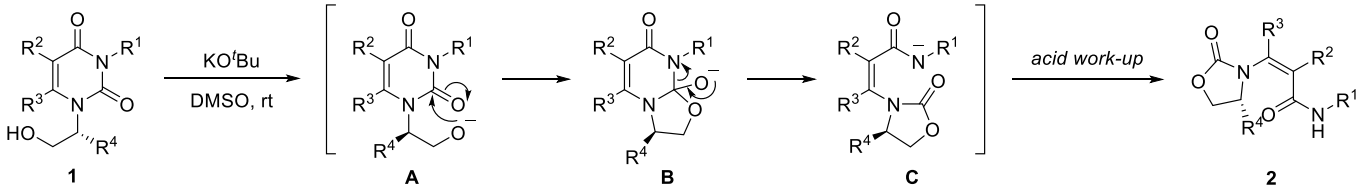
1a, 1h–1p **2a, 2h–2p**

Entry	Substrate	R^1	R^2	R^3	n	Product	Isolated yield (%)
1[a]	**1a**	H	H	H	1	**2a**	90
2	**1h**	Me	H	H	1	**2h**	51
3[b]	**1i**	F	H	H	1	**2i**	83

4	**1j**	Br	H	H	1	**2j**	45
5	**1k**	H	Me	H	1	**2k**	0
6	**1l**	Me	H	H	0	**2l**	0
7	**1m**	H	H	H	2	**2m**	0
8	**1n**	H	H	H	3	**2n**	0
9	**1o**	H	H	Ph	1	**2o**	95
10	**1p**	H	H	Bn	1	**2p**	99

[a] 3 h. [b] 6 h.

A plausible reaction mechanism is outlined in Scheme 2. Alkoxide **A** is initially generated *in situ* by treating **1** with KO^{t}Bu. A bicyclic tetrahedral intermediate **B** is produced through the intramolecular nucleophilic attack of alkoxide **A** on the carbon atom at the 2-position of the uracil ring. Subsequent release of an amide anion from intermediate **B** caused uracil ring-opening, affording the negatively charged 2-oxazolidinone **C**. Finally, protonation of the amide nitrogen during acidic work-up gives the corresponding neutral 2-oxazolidinone derivative **2**. EWGs at the 3-position of the uracil ring likely stabilize the amide, thus promoting expulsion of the amide anion from the bicyclic tetrahedral intermediate **B**.



Scheme 2. A plausible reaction mechanism for the ring transformation of uracils to 2-oxazolidinones

In summary, here we described a novel ring transformation of uracils to 2-oxazolidinones by opening the pyrimidine ring between C2 and N3, followed by ring closure between C2 and the neighbouring hydroxy group. Treatment of N^3-EWG-protected uracil derivatives bearing a 2-hydroxyethyl moiety at the 1-position with base under anhydrous conditions affords the corresponding oxazolidinone at room temperature. Under optimized KO^{t}Bu–DMSO conditions, various N^3-benzoyluracil derivatives with a substituent at the 5-position or on the hydroxyethyl moiety provide the corresponding oxazolidinone in moderate to excellent yield. We anticipate that this reaction will offer an attractive synthetic tool for various functional molecules. Our attempts to identify further undiscovered reactions on uracil derivatives is in progress.

EXPERIMENTAL

General

All reactions were carried out under an argon atmosphere, unless otherwise noted. All reagents and solvents were purchased from commercial vendors and used without further purification, unless indicated otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a JNM ECS-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) were expressed in parts per million and internally referenced (7.26 ppm for $CDCl_3$ or 2.49 ppm for DMSO-d_6 for ^{1}H NMR and 77.0 ppm for $CDCl_3$ or 39.5 ppm for DMSO-d_6 for ^{13}C NMR). Electrospray ionization (ESI) mass spectra were taken on a JMS T100LP instrument or a Waters Xevo Q-Tof mass spectrometer. Flash column chromatography was performed using silica gel 60N [spherical neutral (63-210 μm)] from Kanto Chemical Co., Inc. or silica gel PSQ 100B from Fuji Silysia Chemical Co., Ltd.

General procedure for the ring transformation of uracil derivatives

KO^{t}Bu (12.5 mg, 100 μmol) was added to a solution of uracil derivatives (100 μmol) in DMSO (500 μL) at 0 °C, and the mixture was stirred at room temperature. After a certain period, H_2O (500 μL) and 1 M HCl (500 μL) was added at 0 °C. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding 2-oxazolidinone derivative.

(*Z*)-*N*-[3-(2-Oxooxazolidin-3-yl)acryloyl]benzamide (2a) : Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.0 (s, 1H), 7.89 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 6.98 (d, J = 10.4 Hz, 1H), 5.88 (d, J = 10.4 Hz, 1H), 4.27 (t, J = 8.0 Hz, 2H), 3.95 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 164.8, 156.4, 134.8, 133.4, 132.6, 128.5, 128.3, 101.8, 63.3, 45.0; HRMS (ESI) *m/z* Calcd for $[M(C_{13}H_{12}N_2O_4) + Na]^+$: 283.0695. Found: 283.0678.

(*Z*)-*N*-(2,4-Dinitrophenyl)-3-(2-oxooxazolidin-3-yl)acrylamide (2e) : Pale green solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.9 (s, 1H), 8.67 (d, J = 1.6 Hz, 1H), 8.51 (dd, J = 9.1 Hz, 1.6 Hz, 1H), 7.90 (d, J = 9.1 Hz, 2H), 6.99 (d, J = 9.8 Hz, 1H), 5.45 (d, J = 9.8 Hz, 1H), 4.40 (t, J = 8.0 Hz, 2H), 3.98 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 156.4, 142.3, 136.9, 135.2, 128.5, 124.9, 121.2, 100.3, 63.2, 45.3; HRMS (ESI) *m/z* Calcd for $[M(C_{12}H_{10}N_4O_7) + Na]^+$: 345.0447. Found: 345.0449.

***tert*-Butyl (*Z*)-(3-(2-oxooxazolidin-3-yl)acryloyl)carbamate (2f) :** Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.10 (d, J = 10.6 Hz, 1H), 5.93 (d, J = 10.6 Hz, 1H), 4.43 (t, J = 8.3 Hz, 2H), 4.11 (t, J = 8.3 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 156.4, 150.6, 134.3, 101.1, 80.5, 63.2, 45.0, 27.8; HRMS (ESI) *m/z* Calcd for $[M(C_{11}H_{16}N_2O_5) + H]^+$: 257.1137. Found: 257.1135.

(*Z*)-3-(2-Oxooxazolidin-3-yl)-*N*-(pivaloyl)acrylamide (2g) : Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.1 (s, 1H), 8.58 (d, J = 10.0 Hz, 1H), 5.85 (d, J = 10.0 Hz, 1H), 4.40 (t, J = 7.9 Hz, 2H), 3.87 (t, J = 7.9 Hz, 2H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 165.1, 156.4, 134.2, 102.1, 63.2, 44.8, 26.8, 26.3; HRMS (ESI) *m/z* Calcd for [M($C_{11}H_{16}N_2O_4$) + H]$^+$: 241.1188. Found: 241.1152.

(*Z*)-*N*-(2-Methyl-3-(2-oxooxazolidin-3-yl)acryloyl)benzamide (2h) : Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.2 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 1.6 Hz, 1H), 4.34 (t, J = 8.0 Hz, 2H), 3.62 (t, J = 8.0 Hz, 2H), 1.93 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6); 170.1, 166.3, 155.9, 132.9, 132.9, 128.5, 128.5, 124.6, 113.9, 62.7, 43.7, 18.3; HRMS (ESI) *m/z* Calcd for [M($C_{14}H_{14}N_2O_4$) + Na]$^+$: 297.0851. Found: 297.0834.

(*E*)-*N*-(2-Fluoro-3-(2-oxooxazolidin-3-yl)acryloyl)benzamide (2i) : Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.48 (d, J = 19.6 Hz, 1H), 4.48 (t, J = 7.9 Hz, 2H), 4.33 (t, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); 168.4, 156.2 (d, J = 40.0 Hz), 148.2, 138.8 (d, J = 235 Hz), 135.8, 132.3 (d, J = 33.3 Hz), 130.8, 130.6, 129.6, 58.2, 50.9; HRMS (ESI) *m/z* Calcd for [M($C_{13}H_{11}FN_2O_4$) + Na]$^+$: 301.0601. Found: 301.0575.

(*E*)-*N*-(2-Bromo-3-(2-oxooxazolidin-3-yl)acryloyl)benzamide (2j) : Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.66–7.61 (m, 2H), 7.53 (t, J = 7.6 Hz, 2H), 4.46 (t, J = 8.0 Hz, 2H), 4.07 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 164.6, 160.4, 155.5, 136.2, 133.5, 132.6, 129.2, 127.7, 93.3, 63.1, 45.0; HRMS (ESI) *m/z* Calcd for [M($C_{13}H_{11}BrN_2O_4$) + Na]$^+$: 360.9800. Found: 360.9787.

(*Z*)-*N*-[(*R*)-3-(2-Oxo-4-phenyloxazolidin-3-yl)acryloyl]benzamide (2o) : Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.26 (t, 7.8 Hz, 1H), 7.19–7.13 (m, 4H), 6.11 (d, J = 9.6 Hz, 1H), 5.86 (dd, J = 9.6 Hz, 4.7 Hz, 1H), 4.79 (t, J = 8.8 Hz, 1H), 4.20 (dd, J = 8.8 Hz, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.6, 156.2, 137.2, 133.2, 133.1, 132.7, 129.0, 128.9, 128.8, 127.4, 126.6, 103.2, 70.7, 58.7; HRMS (ESI) *m/z* Calcd for [M($C_{19}H_{16}N_2O_4$) + Na]$^+$: 359.1008. Found: 359.0982.

(*Z*)-*N*-[(*R*)-3-(2-Oxo-4-benzyloxazolidin-3-yl)acryloyl]benzamide (2p) : Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.87 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.29–7.20 (m, 3H), 7.15 (d, J = 6.4 Hz, 2H), 6.45 (d, J = 10.4 Hz, 1H), 5.40–5.36 (m, 1H), 4.25–4.15 (m, 2H), 3.06 (dd, J = 14.0 Hz, 3.6 Hz, 1H), 2.49 (dd, J = 14.0 Hz, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 165.5, 155.8, 135.6, 135.0, 133.3, 132.8, 129.4, 129.0, 129.0, 127.7, 127.3, 100.4, 66.3, 56.1, 36.1; HRMS (ESI) *m/z* Calcd for [M($C_{20}H_{18}N_2O_4$) + Na]$^+$: 373.1164. Found: 373.1153.

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8. Recrystallization of **2a** from MeOH and EtOAc resulted in two types of single crystals that differed in the geometry of the imide moiety: the geometry obtained from EtOAc was *cis-trans* (Figure. S1) while that from MeOH was *trans-trans* (Figure. S3). The X-ray crystallographic coordinates for structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 1976179 for **2a (*cis-trans*)** and 1976180 for **2a (*trans-trans*)**.
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