JOC The Journal of Organic Chemistry

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Synthesis of Oxazoles from Enamides via Phenyliodine Diacetate-Mediated Intramolecular Oxidative Cyclization

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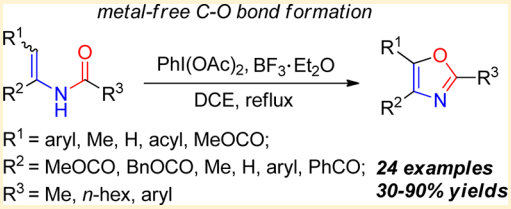
Supporting Information

ABSTRACT: A group of functionalized oxazoles were synthesized in moderate to good yields from enamides via phenyliodine diacetate (PIDA)-mediated intramolecular cyclization. The main advantageous features of the present method include its broad substrate scope and the heavy-metal-free characteristic of the oxidative carbon−oxygen bond formation process.



INTRODUCTION

Presented in many biologically active natural products and pharmaceutical agents, the oxazole skeleton is an important heterocyclic motif.[1] For example, both bengazole A[2] (a potent antifungal marine natural product) and oxaprozin[3] (a non-steroidal anti-inflammatory drug) possess an oxazole subunit in their chemical structure (Figure 1). Accordingly, there exists a large and versatile selection of methods for the synthesis of this important class of compounds.[4] Among them, annulation of enamide derivatives provides a convenient access to oxazole compounds through intramolecular carbon−oxygen bond formation. For examples, β-alkoxy-β-ketoenamides can undergo a TFA-mediated cyclization to afford 5-acetyloxazole derivatives (Figure 2, path a).[5] Glorius and co-workers[6] have developed a copper-catalyzed preparation of 2,5-disubstituted oxazoles from primary amides reacting with 1,2-dihalogenated olefins, which involves the formation of a halogen-substituted enamide intermediate (Figure 2, path b). A similar enamide substrate, i.e., an *N*-acyl-β-halodehydroaminobutyric acid derivative, can also cyclize to oxazole-4-carboxylate via a base-mediated dehalogenation reaction (Figure 2, path c).[7] However, the electron-withdrawing carbonyl substituent in the enamide substrates seems to be indispensable. In 1948, Cornforth reported the formation of oxazoles from enamide derivatives, such that upon treatment of α-hexanoylamino-β-ethylthioacrylic acid with mercuric chloride, 2-amyloxazole could be achieved in a low yield (Figure 2, path d).[8] Moreover, it was found that 5-(subsituted amino)oxazole compounds could be formed from the reaction of an enamide compound, i.e., 2-acylamino-3,3-dihaloacrylonitrile, with amines.[9] The analogous 5-(subsituted mercapto)oxazole compounds could also be prepared from 2-acylamino-3,3-bis(substituted mecapto)-acrylonitrile[10] and polarized ketene dithioacetals[11] in the presence of silver compounds (Ag_2O, Ag_2CO_3 or AgOAc) (Figure 2, path e). Buchward et al[12] have reported a two-step, one-pot preparation of oxazoles from vinyl halides and primary amides, which consists of the formation of an enamide intermediate through copper-catalyzed amidation of vinyl halides, followed by iodine-mediated intramolecular cyclization and elimination of HI under basic conditions (Figure 2, path f). Most recently, a copper(II)-catalyzed oxidative cyclization of enamides to 2,5-disubstituted oxazoles via vinylic C−H bond functionalization has also been described by the same group as the complement of the previous work.[13] Stahl and co-workers[14]

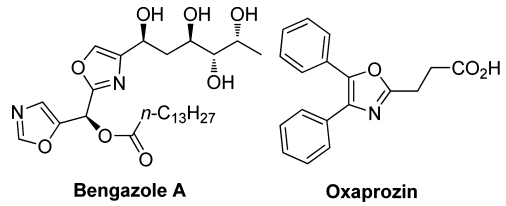


Figure 1. Representative oxazoles in natural products and pharmaceutical agents.

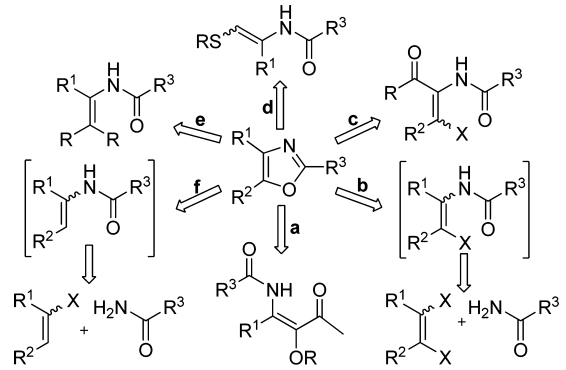


Figure 2. General strategies for the synthesis of oxazoles from enamide derivatives.

Received: September 21, 2012
Published: October 29, 2012

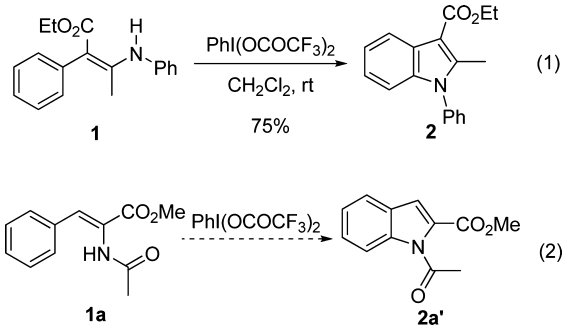
reported the process of a series of enamide compounds, prepared via Ru-catalyzed anti-Markovnikov hydroamidation of alkynes, being converted to 3-nonsubstituted oxazoles via copper(II)-mediated oxidative cyclization.

In recent decades, hypervalent iodine(III) regents have received considerable attention due to their attractive characteristics, such as ready availability, nontoxicity, environmental benignity, while displaying similar reactivities as the heavy metal congeners, such as Hg(II), Tl(III), and Pb(IV) in many oxidative organic transformation.[15] Their unique properties offer promising applications in facilitating metal-free oxidative reactions, as they have shown to efficiently take the place of the highly toxic heavy metals as oxidants. Various *N*-containing heterocycles have been accessed by using hypervalent iodine(III) oxidants to realize the oxidative C−N,[16] N−N,[17] N−S[18] or even C−C[19] bond formation. In our laboratory, we have successfully realized the construction of indole,[16b,19c,20] azirine,[21] and 2-trifluoromethyl oxazole[22] from the reaction of enamine derivatives with hypervalent iodine reagent. As a continuation of our work, we report herein the efficient syntheses of a series of variously functionalized oxazoles from the reactions of enamides with phenyliodine diacetate.[23]

RESULTS AND DISCUSSION

In our previous work, the enamine substrate **1** was successfully converted to the *N*-arylated indole framework **2** through a phenyliodine bis(trifluoroacetate) (PIFA)-mediated intramolecular oxidative cyclization (Scheme 1, eq 1).[16b] This method

Scheme 1. Proposed Route to Access Indole-2-carboxylic Acid Esters Based on the Previously Reported PIFA-Mediated Synthesis of Indole-3-carboxylic Acid Ester

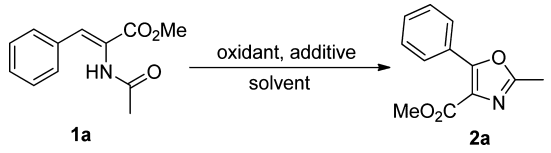


was found to be very useful for the synthesis of *N*-substituted indole compounds bearing a cyano or ethoxycarbonyl group at 3-position. Considering that indole-2-carboxylic acid ester is also a class of biologically important compounds,[24] we became interested in investigating whether the readily available enamide substrate, i.e., (*Z*)-methyl 2-acetamido-3-phenylacrylate (**1a**), could also undergo the similar hypervalent iodine-mediated oxidative C−N bond formation to conceivably give the indole-2-carboxylic acid esters (**2a′**) (Scheme 1, eq 2). To our surprise, no reaction occurred when enamide **1a** was subjected to the identical conditions for the cyclization of enamine **1**, but some reaction did take place after the reaction temperature was raised to reflux. But unfortunately, no desired indole product was formed, except for the oxazole **2a** obtained in a very low yield. The structure of this unexpected oxazole compound was firmly established by X-ray crystal analysis (see Supporting Information for details). This result clearly indicates that when there is no substitution at the *β*-position of enamide **1a**, the intramolecular C−O bond formation is favored over aromatic C−N bond formation in the presence of hypervalent iodine(III)-reagent.

Considering that the yield obtained for **2a** was fairly low, **1a** was used as a model substrate to further optimize the reaction parameters. By changing the solvent to DCE and keeping the temperature at reflux, the product yield was improved. However, the yield was still far from satisfactory because of the formation of other unidentified byproducts. The use of the less potent PIDA diminished the formation of the byproducts, which led to a slight improvement of the product yield. Another hypervalent iodine(III) reagent, i.e., PhI=O, was also studied but was found ineffective for this conversion. Our further study was focused on improving the yield by the introduction of some additive, such as $BF_3{\cdot}Et_2O$ or TFA, which have been well-known for their ability to active the hypervalent iodine(III) reagent.[25] The result showed that when **1a** was subjected to PIDA in the presence of 1.0 equiv of $BF_3{\cdot}Et_2O$, the desired product **2a** could be obtained in a yield of 54%. Increasing the dosage of $BF_3{\cdot}Et_2O$ to 2.0 equiv furnished oxazole **2a** in an excellent yield of 90%. However, a lower yield was observed when the amount of $BF_3{\cdot}Et_2O$ was further increased to 3.0 equiv. TFA was also investigated but was found not as effective as $BF_3{\cdot}Et_2O$. Further solvent screening shows that no other solvent, including toluene, acetonitrile, TFE or ethyl acetate, is superior to DCE.

Under the optimal reaction conditions (Table 1, entry 7), the generality of the method was investigated. The enamides **1b−d**,

Table 1. Optimization of Iodine(III)-Mediated Annulation of Enamides[a]



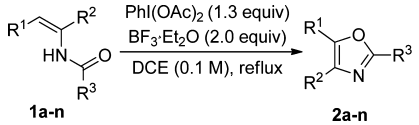
entry	oxidant	additive (equiv)	solvent	*T* (°C)	time (h)	yield (%)[b]
1	PIFA	none	DCM	reflux	1	7
2	PIFA	none	DCE	reflux	1	13
3	PIDA	none	DCE	reflux	1	15
4	PhIO	none	DCE	reflux	1	0
5	PIDA	$BF_3{\cdot}Et_2O$ (1.0)	DCE	reflux	1	54
6	PIFA	$BF_3{\cdot}Et_2O$ (1.0)	DCE	reflux	1	31
7	**PIDA**	**$BF_3{\cdot}Et_2O$ (2.0)**	**DCE**	**reflux**	**1**	**90**
8	PIDA	$BF_3{\cdot}Et_2O$ (3.0)	DCE	reflux	1	70
9	PIDA	CF_3CO_2H (3.0)	DCE	reflux	1	27
10	PIDA	$BF_3{\cdot}Et_2O$ (2.0)	toluene	85	12	trace
11	PIDA	$BF_3{\cdot}Et_2O$ (2.0)	CH_3CN	reflux	4	21
12	PIDA	$BF_3{\cdot}Et_2O$ (2.0)	TFE	reflux	3	37
13	PIDA	$BF_3{\cdot}Et_2O$ (2.0)	EtOAc	reflux	1	49

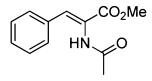
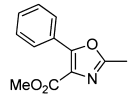
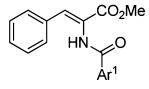
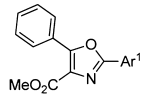
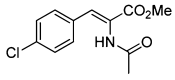
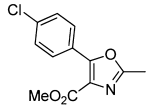
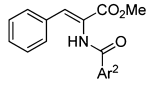
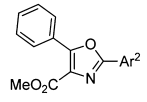
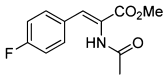
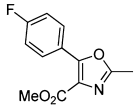
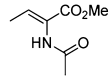
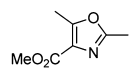
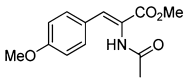
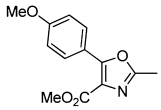
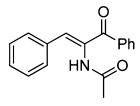
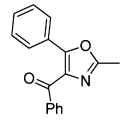
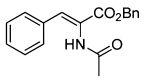
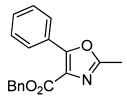
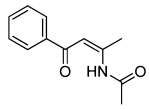
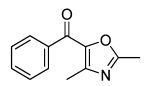
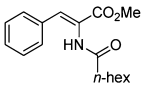
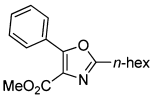
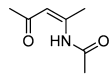
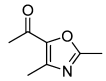
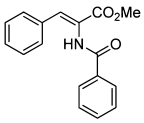
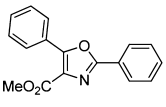
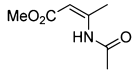
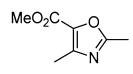
[a]Reaction conditions: **1a** (0.5 mmol), oxidant (0.65 mmol) in solvent (5 mL). [b]Isolated yields.

analogues of **1a** that bear an ester group, were further studied since they are readily available through the reactions of substituted benzaldehyde with glycine derivatives. Each of the substrates, containing either an electron-deficient or electron-rich substituent on the benzene ring, was converted to the corresponding oxazoles **2b−d** in good to excellent yields.

dx.doi.org/10.1021/jo302073e | J. Org. Chem. 2012, 77, 10353−10361

Table 2. Synthesis of Oxazoles via PIDA-Mediated Annulation of Enamides 1[a]



entry	enamide	oxazole	time (h)	yield (%)[b]	entry	enamide	oxazole	time (h)	yield (%)[b]
1	 **1a**	 **2a**	1	90	8[c]	 **1h**	 **2h**	3	89
2	 **1b**	 **2b**	2	90	9[d]	 **1i**	 **2i**	2.5	84
3	 **1c**	 **2c**	1.5	74	10	 **1j**	 **2j**	1.5	37
4	 **1d**	 **2d**	0.5	85	11	 **1k**	 **2k**	0.5	76
5	 **1e**	 **2e**	1	78	12	 **1l**	 **2l**	0.5	86
6	 **1f**	 **2f**	0.5	81	13	 **1m**	 **2m**	0.5	55
7	 **1g**	 **2g**	2	83	14	 **1n**	 **2n**	0.5	88

[a]General conditions: **1** (1.0 equiv), $BF_3{\cdot}Et_2O$ (2.0 equiv), PIDA (1.3 equiv) in DCE under reflux. [b]Isolated yields. [c]Ar^1 herein refers to 4-chlorophenyl group. [d]Ar^2 herein refers to 3,4-dimethoxyphenyl group.

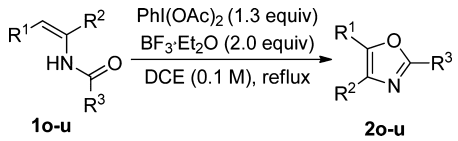
Furthermore, different ester group such as benzoyloxycarbonyl group was also applicable to the method.

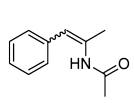
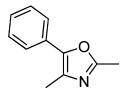
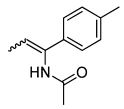
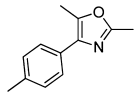
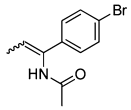
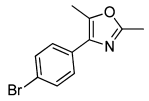
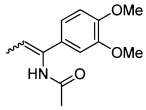
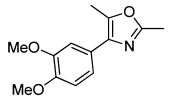
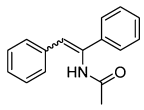
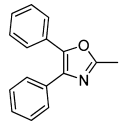
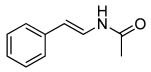
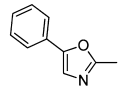
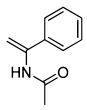
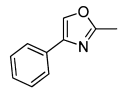
Further study (Table 2) shows that the acetyl group in the substrate can be changed into a long-chained acyl group or bulky aroyl group, which makes this method applicable to the synthesis of various 2-alkyl and 2-aryl oxazoles. When the β-aryl group in the substrate was replaced by an alkyl group, the corresponding enamide **1j** also afforded the desired oxazole **2j**, but in a much lower yield. The successful conversion of **1k** to **2k** implies that the ester group in the substrate can also be replaced with a carbonyl ketone moiety. Furthermore, the electron-withdrawing carbonyl substitution at the α-position in the enamide substrate can also be switched to the β-position, which renders the synthesis of the oxazole compounds bearing a carbonyl group at the 5-position.

The result of our further study (Table 3) shows that the α-ester group in the enamide substrate is not indispensable for the reaction to occur. Under the reaction conditions, both *Z* and *E* isomers of enamide **1o** were converted to the cyclized oxazole **2o** in almost the same yield, which indicates that the configuration of the substrate has little influence on the outcome of yield. For α-aryl enamides **1p−r**, the cyclization occurs smoothly to afford the desired 4-aryloxazole **2p−r** in good yields. The method can be further applied to the preparation of 4,5-diphenyloxazole **2s**. For enamides **1t** and **1u**, bearing no substitution at either the α- or β-position of the

dx.doi.org/10.1021/jo302073e | J. Org. Chem. 2012, 77, 10353−10361

Table 3. Further Synthesis of Variously Functionalized Oxazoles[a]



entry	enamide	oxazole	time (h)	yield (%)[b]
1			0.5	50/48
	***Z*-1o/*E*-1o**	**2o**		
2			0.5	82
	1p	**2p**		
3			1	82
	1q	**2q**		
4			0.5	71
	1r	**2r**		
5			2	70
	1s	**2s**		
6			2	56
	1t	**2t**		
7			0.5	30
	1u	**2u**		

[a]General conditions: see Table 2. [b]Isolated yields.

enamide substrates, the reaction affords the desired 4-nonsubstituted or 5-nonsubstituted oxazoles respectively. But **2u** was obtained in a relatively low yield because of the formation of more byproducts.

One application of this hypervalent iodine(III)-mediated synthesis of oxazole is to synthesize oxaprozin (**6a**). Adopting the known method,[26] the required enamide substrate **4a** can be prepared from the readily available ketone **3a** in 77% yield. Subjecting **4a** to our optimized cyclization conditions conveniently furnished the oxazole intermediate **5a**, which undergoes the known basic hydrolysis[27] to afford oxaprozin in excellent yield (Scheme 2). This approach can be utilized to synthesize other oxaprozin analogues such as **6b** and **6c**, which can bear various substituents on the two phenyl rings.

A possible mechanistic pathway for this iodine(III)-mediated cyclization of enamide is shown in Scheme 3. First, the iodo intermediate **B** was formed from the reaction of the enamide substrate **A** with PIDA by losing one molecule of AcOH. Then the imine intermediate **B** is isomerized into the enamide **C**. When substituent R^2 represents an electron-withdrawing substituent, such as a carbonyl group, nucleophilic addition of the carbonyl oxygen atom to the sp^2 carbon bonded to the hypervalent iodine in **D1** occurred, forming five-membered intermediate **E1**. Subsequent reductive elimination of PhI and AcOH provided product **F**. Alternatively, when substituent R^2 is not electron-withdrawing and represents a methyl group or hydrogen atom, intermediate **D2** may undergo intramolecular cyclization to give the six-membered intermediate **E2**. Finally, the reductive elimination of PhI from **E2** realized the oxidative C−O bond formation to furnish the title oxazole compound **F** (Scheme 3).

CONCLUSION

In summary, we have developed a new hypervalent iodine(III)-mediated synthesis of highly functionalized oxazoles starting from the readily available enamides. Differing from the traditional transition-metal participated heterofunctionalization of C−H bonds, this approach realizes the synthesis of variously functionalized oxazoles through oxidative carbon−oxygen bond formation free of the catalytic transition metals.

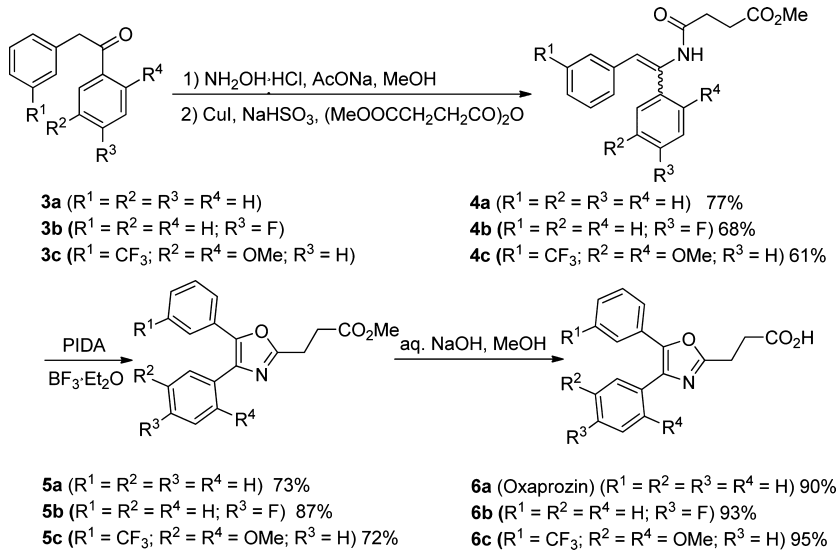
EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz instrument (100 MHz for ^{13}C NMR) at 25 °C. Chemical shift values were given in ppm and referred to the internal standard TMS set as 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; qui, quintuplet; m, multiplet; and dd, doublet of doublets. The coupling constants, *J*, are reported in hertz (Hz). Low-resolution mass spectrometry (ESI) was performed on an ion-trap spectrometer. High resolution mass spectra (HRMS) were obtained on a Q-TOF microspectrometer. Melting points were determined with a national micromelting point apparatus without corrections. TLC plates were visualized by exposure to ultraviolet light. Toluene, THF, DCM and DCE were dried by CaH_2 before use. Other reagents and solvents were purchased at reagent grade and used without further purification. All reactions were performed in standard glassware, heated at 70 °C for 3 h before use. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of petroleum ether (PE) and ethyl acetate (EtOAc).

General Procedures for the Preparation of Substrates. *1. General Procedure for the Preparation of **1a−e** and **1g−i**.* Adapted from a previously reported procedure with some modifications.[28] To a suspension of *N*-acylglycine (50 mmol), sodium acetate (50 mmol), and acetic anhydride (30 mL) was added the aromatic aldehyde (50 mmol). The reaction mixture was stirred at room temperature for 1 h and then heated to 80 °C. After 12 h, the reaction mixture was cooled down to room temperature, mixed with water (0.5 L) and stirred at room temperature for 1 h. The insoluble material was separated by filtration. The alcohol (20 mL) solution of the insoluble material (10 mol) and triethylamine (2 mL) was heated under reflux for 3 h. The solvent was evaporated, and the residue was suspended in water and extracted with EtOAc (4 × 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and then concentrated by a rotary evaporator. The crude product was purified by flash column chromatography (EtOAc/PE) to give the desired compounds.

dx.doi.org/10.1021/jo302073e | J. Org. Chem. 2012, 77, 10353−10361

Scheme 2. Synthesis of Oxaprozin Analogues via PIDA-Mediated Cyclization



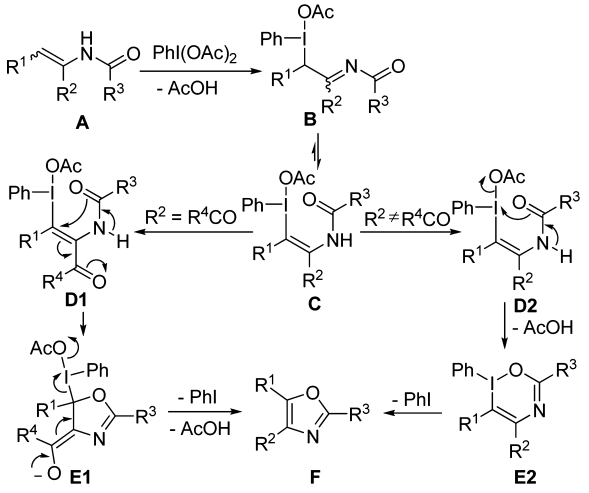
3a ($R^1 = R^2 = R^3 = R^4 = H$)
3b ($R^1 = R^2 = R^4 = H$; $R^3 = F$)
3c ($R^1 = CF_3$; $R^2 = R^4 = OMe$; $R^3 = H$)

4a ($R^1 = R^2 = R^3 = R^4 = H$) 77%
4b ($R^1 = R^2 = R^4 = H$; $R^3 = F$) 68%
4c ($R^1 = CF_3$; $R^2 = R^4 = OMe$; $R^3 = H$) 61%

5a ($R^1 = R^2 = R^3 = R^4 = H$) 73%
5b ($R^1 = R^2 = R^4 = H$; $R^3 = F$) 87%
5c ($R^1 = CF_3$; $R^2 = R^4 = OMe$; $R^3 = H$) 72%

6a (Oxaprozin) ($R^1 = R^2 = R^3 = R^4 = H$) 90%
6b ($R^1 = R^2 = R^4 = H$; $R^3 = F$) 93%
6c ($R^1 = CF_3$; $R^2 = R^4 = OMe$; $R^3 = H$) 95%

Scheme 3. Proposed Mechanistic Pathway



(Z)-Methyl 2-acetamido-3-phenylacrylate (**1a**). Yield: 56%, 6.77 g, white solid, mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 6.0 Hz, 2H), 7.42−7.29 (m, 4H), 7.02 (br s, 1H), 3.85 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 165.8, 133.7, 132.4, 129.7, 129.5, 128.6, 124.4, 52.7, 23.3; HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_3^+$ [M + Na^+] 242.0788, found 242.0791.

(Z)-Methyl 2-acetamido-3-(4-chlorophenyl)acrylate (**1b**).[29] Yield: 52%, 6.58 g, white solid, mp 169−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.29 (m, 5H), 7.10 (s, 1H), 3.85 (s, 3H), 2.13 (s, 3H).

(Z)-Methyl 2-acetamido-3-(4-fluorophenyl)acrylate (**1c**).[29] Yield: 62%, 7.34 g, white solid, mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 3H), 7.06 (m, 3H), 3.85 (s, 3H), 2.13 (s, 3H).

(Z)-Methyl 2-acetamido-3-(4-methoxyphenyl)acrylate (**1d**). Yield: 24%, 3.26 g, white solid, mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.41 (m, 3H), 6.98 (s, 1H), 6.89 (d, J = 8.3 Hz, 2H), 3.83 (s, 6H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.1, 160.5, 133.4, 131.8, 126.1, 122.3, 114.0, 55.3, 52.4, 23.1; HRMS (ESI) m/z calcd for $C_{13}H_{15}NNaO_4^+$ [M + Na^+] 272.0893, found 272.0898.

(Z)-Benzyl 2-acetamido-3-phenylacrylate (**1e**). Yield: 53%, 4.21 g, white solid, mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.30 (m, 11H), 7.14 (br s, 1H), 5.26 (s, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 165.2, 135.6, 133.7, 132.6, 129.7, 129.5, 128.6, 128.6, 128.4, 128.4, 124.4, 67.5, 23.4; HRMS (ESI) m/z calcd for $C_{18}H_{17}NNaO_3^+$ [M + Na^+] 318.1101, found 318.1106.

(Z)-Methyl 2-benzamido-3-phenylacrylate (**1g**).[30] Yield: 50%, 3.52 g, white solid, mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.4 Hz, 2H), 7.77 (br s, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.52−7.43 (m, 5H), 7.33 (m, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 133.8, 133.5, 132.2, 132.1, 129.7, 129.5, 128.7, 128.6, 127.5, 124.4, 52.7; One carbon was missing due to overlapping.

(Z)-Methyl 2-(4-chlorobenzamido)-3-phenylacrylate (**1h**). Yield: 55%, 4.33 g, white solid, mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 7.0 Hz, 3H), 7.41 (d, J = 8.4 Hz, 2H), 7.32 (m, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.0, 138.4, 133.6, 132.8, 131.7, 129.7, 129.6, 129.0, 128.9, 128.6, 124.3, 52.8; HRMS (ESI) m/z calcd for $C_{17}H_{14}Cl^{35}NNaO_3^+$ [M + Na^+] 338.0554, found 338.0555.

(Z)-Methyl 2-(3,4-dimethoxybenzamido)-3-phenylacrylate (**1i**). Yield: 67%, 5.71 g, white solid, mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.53−7.45 (m, 3H), 7.45−7.38 (m, 2H), 7.32 (m, 3H), 6.88 (dd, J = 8.3, 3.1 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.4, 152.3, 149.0, 133.8, 131.7, 129.7, 129.4, 128.6, 125.9, 124.8, 120.4, 110.9, 110.3, 56.0, 55.9, 52.7; HRMS (ESI) m/z calcd for $C_{19}H_{19}NNaO_5^+$ [M + Na^+] 364.1155, found 364.1155.

2. General Procedure for the Preparation of **1f**. Adapted from a previously reported procedure with some modifications.[31] To a suspension of 2-heptanamidoacetic acid (8 mmol) in THF (30 mL) was added dicyclohexylcarbodiimide (8 mmol). The reaction mixture was stirred at room temperature overnight and then filtered and concentrated on a rotary evaporator. The crude product was purified by flash column chromatography (EtOAc/PE). Then the product was added to the suspension of sodium acetate (5 mmol), acetic anhydride (3 mL) and aromatic aldehyde (5 mmol). The reaction mixture was stirred at room temperature for 1 h and then heated to 80 °C. After 12 h, the reaction mixture was cooled down to room temperature, mixed with water (50 mL) and stirred at room temperature for 1 h. The insoluble material was separated by filtration. The methanol (10 mL) solution of the insoluble material (5 mmol) and triethylamine (1 mL) was heated under reflux for 3 h. The solvent was evaporated, and the residue was suspended in water and extracted with EtOAc (4 × 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and then concentrated by a rotary evaporator. The crude product was purified by flash column chromatography (EtOAc/PE) to give the desired compound.

(Z)-Methyl 2-heptanamido-3-phenylacrylate (**1f**). Yield: 44%, 764 mg, white solid, mp 73−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.2 Hz, 2H), 7.32 (d, J = 5.9 Hz, 4H), 7.23 (br s, 1H), 3.81 (s, 3H), 2.30 (t, J = 7.3 Hz, 2H), 1.74−1.56 (m, 2H), 1.29 (br s, 6H), 0.88 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 165.8,

dx.doi.org/10.1021/jo302073e | J. Org. Chem. 2012, 77, 10353−10361

133.8, 132.0, 129.6, 129.3, 128.5, 124.5, 52.6, 36.6, 31.5, 28.9, 25.3, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{24}NO_3^+$ [M + H$^+$] 290.1751, found 290.1754.

3. General Procedure for the Preparation of ***1j, 1k, 1l,m, 1n, 1o, 1p−s, 1t and 1u.*** The desired substrates **1j**,[32] **1k**,[33] **1l,m**,[34] **1n**,[35] **1o**,[34] **1p−s**,[26b] **1t**,[36] and **1u**[26b] were prepared according to the literature procedures. The ratio of the minor and major isomers of the enamide was determined from the ^{1}H NMR spectral data.

*(Z)-Methyl 2-acetamidobut-2-enoate (**1j**).*[32] Yield: 30%, 610 mg, white solid, mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (br s, 1H), 6.82 (q, J = 7.2 Hz, 1H), 3.77 (s, 3H), 2.13 (s, 3H), 1.78 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 165.1, 134.3, 125.9, 52.4, 23.4, 14.8.

*(Z)-N-(3-Oxo-1,3-diphenylprop-1-en-2-yl)acetamide (**1k**).*[37] Yield: 70%, 910 mg, white solid, mp 184−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 2H), 7.63−7.32 (m, 9H), 6.68 (s, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 168.6, 136.9, 133.8, 133.1, 132.5, 130.4, 129.7, 129.4, 129.3, 128.9, 128.3, 23.2.

*(Z)-N-(4-Oxo-4-phenylbut-2-en-2-yl)acetamide (**1l**).*[34] Yield: 43%, 874 mg, white solid, mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ12.81 (br s, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 6.04 (s, 1H), 2.52 (s, 3H), 2.23 (s, 3H).

*(Z)-N-(4-Oxopent-2-en-2-yl)acetamide (**1m**).*[34] Yield: 54%, 761 mg, light yellow solid, mp 43−44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (br s, 1H), 5.33 (s, 1H), 2.37 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H).

*(Z)-Methyl 3-acetamidobut-2-enoate (**1n**).*[35] Yield: 54%, 730 mg, white solid, mp 42−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (br s, 1H), 4.91 (s, 1H), 3.70 (s, 3H), 2.38 (s, 3H), 2.15 (s, 3H).

*(Z)-N-(1-Phenylprop-1-en-2-yl)acetamide (Z-**1o**).*[38] Yield: 70%, 1.30 g, light yellow solid, mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.28 (m, 3H), 7.10−7.24 (m, 3H), 5.71 (s, 1H), 2.30 (s, 3H), 1.99 (m, 3H).

*(E)-N-(1-Phenylprop-1-en-2-yl)acetamide (E-**1o**).*[38] Yield: 10%, 186 mg, white solid, mp 62−63 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.22−7.12 (m, 3H), 7.08 (br s, 1H), 1.98 (s, 3H), 1.97 (s, 3H).

*N-(1-(p-Tolyl)prop-1-en-1-yl)acetamide (**1p**).* Yield: 62%, 1.21 g, white solid (minor/major = 1:1.9); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer δ 7.30 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.71 (br s, 1H), 5.99 (q, J = 6.8 Hz, 1H), 2.35 (s, 3H), 1.82 (d, J = 6.8 Hz, 3H), 1.78 (s, 3H); major isomer δ 7.24 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.95 (br s, 1H), 5.88 (q, J = 6.8 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H), 1.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) minor isomer δ 173.5, 138.1, 135.7, 129.4, 128.1, 125.2, 121.2, 21.1, 20.5, 13.6; major isomer δ 168.4, 137.4, 135.3, 134.0, 129.1, 125.4, 120.2, 23.3, 21.1, 14.0; HRMS (ESI) m/z calcd for $C_{12}H_{15}NNaO^+$ [M + Na$^+$] 212.1046, found 212.1047.

*N-(1-(4-Bromophenyl)prop-1-en-1-yl)acetamide (**1q**).* Yield: 56%, 867 mg, white solid (minor/major = 1:15.2); ^{1}H NMR (400 MHz, DMSO-d_6) minor isomer δ 8.73 (br s, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.20 (q, J = 6.8 Hz, 1H), 2.08 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H); major isomer δ 9.17 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 5.93 (q, J = 6.8 Hz, 1H), 2.00 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) major isomer δ 168.5, 138.1, 134.4, 131.5, 127.6, 120.7, 120.5, 23.1, 14.2. The ^{13}C NMR data of the minor isomer was not collected due to its low concentration; HRMS (ESI) m/z calcd for $C_{11}H_{12}Br^{79}NNaO^+$ [M + Na$^+$] 275.9994, found 275.9997.

*N-(1-(3,4-Dimethoxyphenyl)prop-1-en-1-yl)acetamide (**1r**).* Yield: 46%, 1.12 g, white solid (minor/major = 1:13.9); ^{1}H NMR (400 MHz, DMSO-d_6) minor isomer δ 8.63 (s, 1H), 7.02 (s, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 6.05 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.00 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H); major isomer δ 9.03 (s, 1H), 6.95 (s, 1H), 6.88 (s, 2H), 5.83 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.00 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) major isomer δ 168.1, 148.9, 148.8, 134.8, 131.8, 118.0, 117.9, 111.9, 109.4, 56.0, 55.9, 23.2, 14.3. The ^{13}C NMR data of the minor isomer was not collected due to its low concentration; HRMS (ESI) m/z calcd for $C_{13}H_{18}NO_3^+$ [M + H$^+$] 236.1281, found 236.1284.

*N-(1,2-Diphenylvinyl)acetamide (**1s**).*[38] Yield: 57%, 410 mg, white solid (minor/major = 1:1.9); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer δ 7.59−7.27 (m, 10H), 6.63 (s, 1H), 6.52 (s, 1H), 1.72 (s, 3H); major isomer δ 7.59−7.27 (m, 6H), 7.07−7.05 (m, 3H), 6.93−6.91 (m, 2H), 6.74 (s, 1H), 2.08 (s, 3H).

*(E)-N-Styrylacetamide (**1t**).*[39] Yield: 44%, 480 mg, light yellow solid, mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 14.6, 10.9 Hz, 1H), 7.30 (m, 5H), 7.18 (t, J = 6.8 Hz, 1H), 6.08 (d, J = 14.6 Hz, 1H), 2.11 (s, 3H).

*N-(1-Phenylvinyl)acetamide (**1u**).*[26b] Yield: 68%, 1.17 g, white solid, mp 93−94 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (br s, 1H), 7.48−7.30 (m, 5H), 5.62 (s, 1H), 4.98 (s, 1H), 2.01 (s, 3H).

4. General Procedure for the Preparation of ***4a−4c.*** The desired substrates **4a−4c** were prepared according to the literature procedures.[26]

*Methyl 4-((1,2-diphenylvinyl)amino)-4-oxobutanoate (**4a**).* Yield: 77%, 761 mg, white solid (minor/major = 1:1.2); ^{1}H NMR (400 MHz, DMSO-d_6) minor isomer δ 9.65 (s, 1H), 7.56 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 7.2 Hz, 2H), 7.43−7.27 (m, 6H), 6.73 (s, 1H), 3.60 (s, 3H), 2.72−2.51 (m, 4H); major isomer δ 9.40 (s, 1H), 7.34−7.21 (m, 5H), 7.18 (s, 1H), 7.07 (t, J = 7.2 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 7.6 Hz, 2H), 3.60 (s, 3H), 2.72−2.51 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) mixture δ 173.3, 173.3, 170.9, 170.8, 139.3, 137.2, 137.1, 136.5, 136.5, 134.9, 129.8, 129.3, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 127.7, 126.2, 126.1, 123.1, 51.8, 31.3, 30.5, 29.1, 29.0; Three carbons were missing due to overlapping; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_3^+$ [M + H$^+$] 310.1438, found 310.1441.

*Methyl 4-((1-(4-fluorophenyl)-2-phenylvinyl)amino)-4-oxobutanoate (**4b**).* Yield: 68%, 650 mg, white solid (minor/major = 1:1.2); ^{1}H NMR (400 MHz, DMSO-d_6) minor isomer δ 9.44 (s, 1H), 7.31−7.06 (m, 8H), 6.85 (d, J = 7.2 Hz, 2H), 3.60 (s, 3H), 2.60−2.53 (m, 4H); major isomer δ 9.69 (s, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.31−7.06 (m, 4H), 7.03 (d, J = 7.2 Hz, 1H), 6.69 (s, 1H), 3.60 (s, 3H), 2.62−2.56 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) mixture δ 173.3, 173.2, 170.9, 163.6, 161.2, 137.0, 135.8, 135.6, 135.2 (d, J_{C-F} = 234.9 Hz), 134.6 (d, J_{C-F} = 237.8 Hz), 132.0 (d, J_{C-F} = 8.3 Hz), 129.3, 129.1, 128.8, 128.5, 128.1 (d, J_{C-F} = 8.1 Hz), 127.7, 126.3, 123.0, 117.0, 115.8 (d, J_{C-F} = 21.2 Hz), 115.5 (d, J_{C-F} = 21.3 Hz), 51.8, 31.3, 30.4, 29.0, 28.9; Three carbons were missing due to overlapping; HRMS (ESI) m/z calcd for $C_{19}H_{18}FNNaO_3^+$ [M + Na$^+$] 350.1163, found 350.1165.

*Methyl 4-((1-(2,5-dimethoxyphenyl)-2-(3-(trifluoromethyl)-phenyl)vinyl)amino)-4-oxobutanoate (**4c**).* Yield: 61%, 936 mg, white solid (minor/major = 1:2.3); ^{1}H NMR (400 MHz, DMSO-d_6) minor isomer δ 9.63 (s, 1H), 7.77−7.78 (m, 2H), 7.55 (d, J = 4.4 Hz, 2H), 7.05−6.92 (m, 1H), 6.87 (m, 2H), 6.52 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.57 (s, 3H), 2.51 (s, 4H); major isomer 9.42 (s, 1H), 7.47 (s, 1H), 7.33−7.30 (m, 2H), 7.14 (d, J = 6.0 Hz, 1H), 7.05−6.92 (m, 3H), 6.67 (d, J = 2.8 Hz, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 2.51 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) mixture δ 173.3, 173.2, 170.9, 170.1, 153.9, 153.5, 151.8, 151.7, 138.9, 138.0, 135.6, 134.2, 132.8, 132.3, 129.6, 129.3, 129.4 (q, J_{C-F} = 31.3 Hz), 129.1 (q, J_{C-F} = 30.4 Hz), 126.1, 125.3 (q, J_{C-F} = 243.8 Hz), 124.6 (q, J_{C-F} = 270.9 Hz), 124.2 (q, J_{C-F} = 4.0 Hz), 123.5, 122.2 (q, J_{C-F} = 3.5 Hz), 116.9, 115.7, 115.5, 114.4, 114.1 (q, J_{C-F} = 4.1 Hz), 113.7, 113.5 (q, J_{C-F} = 3.5 Hz), 56.7, 56.3, 56.0, 55.9, 51.8, 51.7, 31.4, 30.5, 29.0, 28.9; One carbon was missing due to overlapping; HRMS (ESI) m/z calcd for $C_{22}H_{22}F_3NNaO_5^+$ [M + Na$^+$] 460.1342, found 460.1343.

5. General Procedure for the Synthesis of Oxazole Derivatives. To a solution of the enamide (2.0 mmol) in dried DCE (20 mL) was added $BF_3{\cdot}Et_2O$ (4.0 mmol). The reaction mixture was heated to reflux, and then PIDA (2.6 mmol) was added in one portion rapidly. After stirring under reflux for 0.5−3 h, the reaction mixture was cooled down to rt, quenched with saturated aqueous $NaHCO_3$, and then extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated by the rotary evaporator. The crude product was purified by flash column chromatography (EA/PE) to give the desired compounds.

*Methyl 2-methyl-5-phenyloxazole-4-carboxylate (**2a**).* Yield: 90%, 446 mg, white solid, mp 76−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.07 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 6.8 Hz, 3H), 3.94 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.8, 155.4, 130.2, 128.4, 128.2, 127.0, 126.6, 52.2, 13.8; HRMS (ESI) m/z calcd for $C_{12}H_{11}NNaO_3^+$ [M + Na$^+$] 240.0631, found 240.0632.

Methyl 5-(4-chlorophenyl)-2-methyloxazole-4-carboxylate (**2b**). Yield: 90%, 445 mg, white solid, mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.9, 154.3, 136.2, 129.4, 128.7, 126.9, 125.4, 52.3, 13.8; HRMS (ESI) m/z calcd for $C_{12}H_{10}ClNNaO_3^+$ [M + Na$^+$] 274.0241, found 274.0243.

Methyl 5-(4-fluorophenyl)-2-methyloxazole-4-carboxylate (**2c**). Yield: 74%, 365 mg, white solid, mp 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.4, 5.2 Hz, 2H), 7.16 (t, J = 8.4 Hz, 1H), 3.94 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 162.4, 161.2 (d, J_{C-F} = 287.9 Hz), 154.6, 130.4 (d, J_{C-F} = 8.4 Hz), 126.3, 123.2, 115.6 (d, J_{C-F} = 21.8 Hz), 52.2, 13.7; HRMS (ESI) m/z calcd for $C_{12}H_{10}FNNaO_3^+$ [M + Na$^+$] 258.0537, found 258.0542.

Methyl 5-(4-methoxyphenyl)-2-methyloxazole-4-carboxylate (**2d**). Yield: 85%, 250 mg, white solid, mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.1, 159.1, 155.7, 129.9, 125.2, 119.5, 113.8, 55.3, 52.1, 13.7; HRMS (ESI) m/z calcd for $C_{13}H_{13}NNaO_4^+$ [M + Na$^+$] 270.0737, found 270.0741.

Benzyl 2-methyl-5-phenyloxazole-4-carboxylate (**2e**).[40] Yield: 78%, 230 mg, light yellow solid, mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.04−7.92 (m, 2H), 7.42 (m, 5H), 7.37−7.29 (m, 3H), 5.39 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 159.9, 155.6, 135.7, 130.1, 128.6, 128.5, 128.35, 128.3, 127.0, 126.7, 66.8, 13.8.

Methyl 2-hexyl-5-phenyloxazole-4-carboxylate (**2f**). Yield: 81%, 233 mg, white solid, mp 32−33 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 8.0, 1.6 Hz, 2H), 7.42−7.50 (m, 3H), 3.93 (s, 3H), 2.85 (t, J = 7.6 Hz, 2H), 1.89−1.77 (m, 2H), 1.42−1.37 (m, 2H), 1.35−1.27 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 162.7, 155.2, 130.1, 128.4, 128.2, 127.1, 126.4, 52.2, 31.3, 28.8, 28.1, 27.0, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{21}NNaO_3^+$ [M + Na$^+$] 310.1414, found 310.1417.

Methyl 2,5-diphenyloxazole-4-carboxylate (**2g**).[41] Yield: 83%, 245 mg, white solid, mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.13 (m, 4H), 7.55−7.44 (m, 6H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 159.8, 155.3, 131.1, 130.4, 128.8, 128.5, 128.4, 1287.0, 127.0, 126.9, 126.3, 52.4.

Methyl 2-(4-chlorophenyl)-5-phenyloxazole-4-carboxylate (**2h**).[41] Yield: 89%, 266 mg, white solid, mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.05 (m, 4H), 7.46−7.51 (m, 5H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 158.9, 155.5, 137.4, 130.5, 129.2, 128.5, 128.4, 128.1, 128.0, 126.8, 124.8, 52.4.

Methyl 2-(3,4-dimethoxyphenyl)-5-phenyloxazole-4-carboxylate (**2i**). Yield: 84%, 251 mg, white solid, mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 6.8 Hz, 2H), 7.74 (dd, J = 8.4, 1.6 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.56−7.43 (m, 3H), 6.96 (d, J = 8.4 Hz, 1H), 4.05−3.92 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 159.9, 155.0, 151.7, 149.2, 130.3, 128.4, 127.8, 127.1, 120.3, 119.1, 111.0, 109.6, 56.2, 56.0, 52.4; One carbon was missing due to overlapping; HRMS (ESI) m/z calcd for $C_{19}H_{17}NNaO_5^+$ [M + Na$^+$] 362.0999, found 362.1004.

Methyl 2,5-dimethyloxazole-4-carboxylate (**2j**). Yield: 37%, 110 mg, white solid, mp 44−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 2.59 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 159.4, 156.2, 127.2, 51.8, 13.7, 11.8; HRMS (ESI) m/z calcd for $C_7H_9NNaO_3^+$ [M + Na$^+$] 178.0475, found 178.0480.

(2-Methyl-5-phenyloxazol-4-yl)(phenyl)methanone (**2k**). Yield: 76%, 198 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.98−7.41(m, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.48−7.38 (m, 5H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 159.1, 154.7, 137.5, 133.8, 133.0, 130.3, 130.1, 128.5, 128.2, 127.7, 127.4, 13.9; HRMS (ESI) m/z calcd for $C_{17}H_{13}NNaO_2^+$ [M + Na$^+$] 286.0838, found 286.0843.

(2,4-Dimethyloxazol-5-yl)(phenyl)methanone (**2l**). Yield: 86%, 260 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 2.55 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 162.6, 147.7, 145.0, 137.1, 132.6, 129.1, 128.3, 14.2, 14.0; HRMS (ESI) m/z calcd for $C_{12}H_{11}NNaO_2^+$ [M + Na$^+$] 224.0682, found 224.0685.

1-(2,4-Dimethyloxazol-5-yl)ethanone (**2m**). Yield: 55%, 160 mg, white solid, mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.46 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 162.3, 145.5, 145.0, 27.4, 14.2, 13.5; HRMS (ESI) m/z calcd for $C_7H_9NNaO_2^+$ [M + Na$^+$] 162.0525, found 162.0526.

Methyl 2,4-dimethyloxazole-5-carboxylate (**2n**). Yield: 88%, 436 mg, white solid, mp 45−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 2.50 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 159.0, 146.1, 137.3, 51.8, 14.1, 13.1; HRMS (ESI) m/z calcd for $C_7H_9NNaO_3^+$ [M + Na$^+$] 178.0475, found 178.0478.

2,4-Dimethyl-5-phenyloxazole (**2o**).[42] Yield: 50% (**Z-1o**), 94 mg, 48%(**E-1o**), 91 mg, white solid, mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 145.1, 131.6, 129.3, 128.7, 127.3, 125.1, 13.9, 13.2.

2,5-Dimethyl-4-(p-tolyl)oxazole (**2p**). Yield: 82%, 406 mg, white solid, mp 42−44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.2 Hz, 2H), 7.21 (d, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.45 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 142.9, 136.7, 134.3, 129.6, 129.2, 126.4, 21.2, 13.8, 11.7; HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO^+$ [M + Na$^+$] 210.0889, found 210.0894.

4-(4-Bromophenyl)-2,5-dimethyloxazole (**2q**). Yield: 82%, 243 mg, light yellow solid, mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.45 (m, 4H), 2.47 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 143.7, 133.4, 131.7, 131.4, 128.0, 121.0, 13.8, 11.8; HRMS (ESI) m/z calcd for $C_{11}H_{10}BrNNaO^+$ [M + Na$^+$] 273.9838, found 273.9838.

4-(3,4-Dimethoxyphenyl)-2,5-dimethyloxazole (**2r**). Yield: 71%, 211 mg, white solid, mp 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 1.6 Hz, 1H), 7.10 (dd, J = 8.0, 1.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 149.1, 148.2, 142.6, 134.1, 125.4, 118.9, 111.2, 110.0, 55.9, 55.9, 13.8, 11.7; HRMS (ESI) m/z calcd for $C_{13}H_{15}NNaO_3^+$ [M + Na$^+$] 256.0944, found 256.0947.

2-Methyl-4,5-diphenyloxazole (**2s**). Yield: 70%, 205 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 6.8 Hz, 2H), 7.58 (d, J = 6.8 Hz, 2H), 7.40−7.27 (m, 6H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 145.3, 135.2, 132.5, 129.1, 128.6, 128.6, 128.4, 128.0, 127.9, 126.5, 14.0; HRMS (ESI) m/z calcd for $C_{16}H_{13}NNaO^+$ [M + Na$^+$] 258.0889, found 258.0890.

2-Methyl-5-phenyloxazole (**2t**).[42] Yield: 56%, 166 mg, light yellow solid, mp 43−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.22 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 151.2, 128.9, 128.3, 128.1, 124.0, 121.7, 14.0.

2-Methyl-4-phenyloxazole (**2u**).[43] Yield: 30%, 148 mg, yellow solid, mp 40−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 140.7, 133.2, 131.2, 128.7, 127.9, 125.4, 13.9.

Methyl 3-(4,5-diphenyloxazol-2-yl)propanoate (**5a**).[3b] Yield: 73%, 101 mg, white solid, mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.65 (m, 2H), 7.57 (dd, J = 8.0, 1.6 Hz, 2H), 7.31−7.39 (m, 6H), 3.74 (s, 3H), 3.22 (t, J = 7.2 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H).

Methyl 3-(4-(4-fluorophenyl)-5-phenyloxazol-2-yl)propanoate (**5b**). Yield: 87%, 281 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.4, 5.2 Hz, 2H), 7.57−7.50 (m, 2H), 7.41−7.28 (m, 3H), 7.05 (t, J = 8.4 Hz, 2H), 3.73 (s, 3H), 3.18 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 162.6 (d, J_{C-F} = 245.9 Hz), 161.8, 145.3, 134.2, 129.7 (d, J_{C-F} = 8.1 Hz), 128.8, 128.7, 128.6, 126.5, 115.6 (d, J_{C-F} = 21.4 Hz), 51.9, 30.9, 23.5; One carbon was missing due to overlapping; HRMS (ESI) m/z calcd for $C_{19}H_{16}FNNaO_3^+$ [M + Na$^+$] 348.1006, found 348.1009.

*Methyl 3-(4-(2,5-dimethoxyphenyl)-5-(3-(trifluoromethyl)-phenyl)oxazol-2-yl)propanoate (**5c**).* Yield: 72%, 591 mg, white solid, mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 6.95 (dd, J = 9.2, 3.2 Hz, 1H), 6.87 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.52 (s, 3H), 3.23 (t, J = 7.6 Hz, 2H), 2.94 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 161.9, 153.8, 150.9, 145.1, 132.7, 130.6 (q, J_{C-F} = 32.0 Hz), 130.1, 128.6, 128.2, 124.1 (q, J_{C-F} = 3.3 Hz), 124.0 (q, J_{C-F} = 270.7 Hz), 122.1 (q, J_{C-F} = 3.9 Hz), 121.9, 116.3, 115.8, 112.3, 55.8, 55.5, 51.9, 30.8, 23.6; HRMS (ESI) m/z calcd for $C_{22}H_{20}F_3NNaO_5^+$ [M + Na^+] 458.1186, found 458.1191.

*6. General Procedure for the Synthesis of **6a−c**.* Adapted from a previously reported procedure with some modifications.[27] To a solution of esters (0.75 mmol) in methanol (2 mL) was added 1 M NaOH (8 mL). The mixture was stirred at 50 °C for 0.5−2.5 h. After cooling to room temperature, the reaction mixture was diluted with 1 M HCl (15 mL), and the products were separated by filtration.

*3-(4,5-Diphenyloxazol-2-yl)propanoic acid (**6a**).*[3b] Yield: 90%, 76 mg, white solid, mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 7.63−7.35 (m, 10H), 3.26−3.00 (m, 4H).

*3-(4-(4-Fluorophenyl)-5-phenyloxazol-2-yl)propanoic acid (**6b**).* Yield: 93%, 216 mg, white solid, mp 161−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.4, 5.6 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.33−7.38 (m, 3H), 7.05 (t, J = 8.8 Hz, 2H), 3.19 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 162.7 (d, J_{C-F} = 246.2 Hz), 162.0, 145.5, 134.0, 129.8 (d, J_{C-F} = 8.1 Hz), 128.7, 128.7, 128.6, 128.2, 126.5, 115.6 (d, J_{C-F} = 21.5 Hz), 30.9, 23.2; HRMS (ESI) m/z calcd for $C_{18}H_{14}FNNaO_3^+$ [M + Na^+] 334.0850, found 334.0851.

*3-(4-(2,5-Dimethoxyphenyl)-5-(3-(trifluoromethyl)phenyl)oxazol-2-yl)propanoic acid (**6c**).* Yield: 95%, 300 mg, white solid, mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 2.8 Hz, 1H), 6.95 (dd, J = 9.0, 2.8 Hz, 1H), 6.87 (d, J = 9.2 Hz, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 3.24 (t, J = 7.2 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 162.2, 153.7, 151.0, 145.3, 132.4, 130.7 (q, J_{C-F} = 31.9 Hz), 129.9, 128.6, 128.3, 123.9 (q, J_{C-F} = 270.8 Hz), 124.3 (q, J_{C-F} = 3.5 Hz), 122.1 (q, J_{C-F} = 3.7 Hz), 121.3, 116.2, 116.0, 112.4, 55.8, 55.5, 30.9, 23.3; HRMS (ESI) m/z calcd for $C_{21}H_{18}F_3NNaO_5^+$ [M+ Na^+] 444.1029, found 444.1033.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all compounds and X-ray structural data of **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the National Natural Science Foundation of China (#21072148) for financial support.

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