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Graphical Abstract

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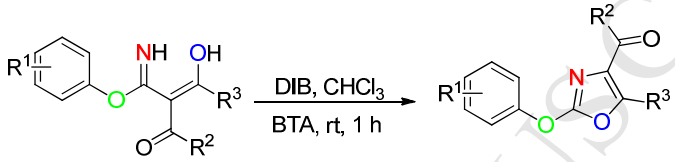

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ABSTRACT

Hypervalent iodine (III)-intermediated direct oxidative rearrangement of 3-hydroxybut-2-enimidates affording oxazoles under mild conditions has been developed. This protocol provides a new methodogy to the synthesis of compounds containing oxazole structure.

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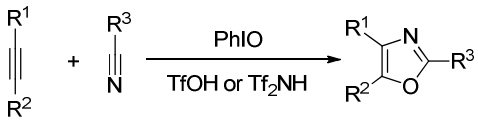
Introduction

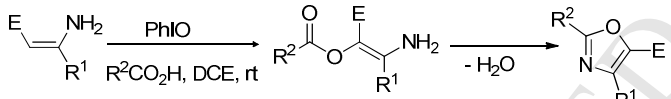
Oxazole fragments are the key building groups in the synthesis of natural product related compunds and act as a significant role with biological and/or pharmaceutical active centers.[1] Especially, 5-substituted oxazole-4-carboxylic acid esters as one of the most valuable intermediate products are used in the synthesis of a large number of biological active compounds such as GW475151.[2] Moreover, 2, 4, 5-trisubstituted oxazoles also were found as an important class of heterocycle structure products with biological activities such as thiopeptide[3] and siphonazole[4]. Therefore, tremendous strategies for the preparation of oxazole motifs have been persued. The synthetic methods of 2, 4, 5-trisubstituted oxazole derivatives compose of metal catalyzed intermolecular or intramolecular cross-coupling[5-9] and metal-free methods[10]. Metal-free methods have received considerable attention in recent decades. Hanzawa et al. reported metal-free annulation procedure for the formation of highly substituted oxazole, which was achieved by the iodine (III)-mediated synthesis of 2, 4, 5-trisubstituted oxazole derivatives (Scheme 1a).[11] Using same hypervalent iodine as oxidant, Zhao et al. disclosed PhIO-mediated intermolecular oxidative coupling and successive intramoleclar nucleophilic addition-elimination towards synthesis of oxazoles (Scheme 1b).[12]

Scheme 1. Synthesis of 2, 4, 5-trisubstituted oxazole derivatives.

a) Hanzawa's work

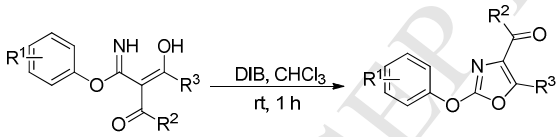


b) Zhao's work



E = CO_2Me, COR^1, CN; R^1 = Me, Ph
R^2 = aryl, alkyl and alkenyl

c) This work

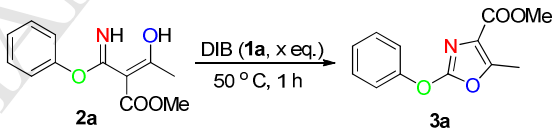


Different to above two pathways, we have reported iodobenzene diacetate (DIB)-mediated oxidative Beckmann-type rearrangement towards synthesis of benzoxazoles and benzimidazoles and extended our method to preparation of chlormidazol and clemizole.[13] We have also developed oxidative coupling reaction of anilines[14] and oxidative cyanation[15-17], covering hypervalent iodine-promoted cyanation of silyl enol ethers via an umpolung strategy[15] and tertiary or secondary aimines via an oxidation/strecker reaction[16,17]. In our preliminary work, the treatment of dicarbonyl compounds and cyanatobenzene led to the formation of 3-hydroxybut-2-enimidate directly[18], which contains the substructures of enol and imine. Inspired by oxidative rearrangement of *ortho*-hydroxylbenzoimine, we envisioned that nucleophilic imine in 3-hydroxybut-2-enimidates are capable of coordinating with electron-deficient iodine of iodobenzene diacetate and nucleophilic attack of enol to nitrogen would result in generation of (iso)oxazole. As expected, we fortunately got the product oxazoles from 3-hydroxybut-2-enimidates via an isoxazole rearrangement. Herein, we would like to report synthesis of 2,4,5-trisubstituted oxazole from 3-hydroxybut-2-enimidate utilizing hypervalent iodine reagent (Scheme 1c).

Results and discussion

We firstly chose methyl 3-hydroxy-2-(imino(phenoxy)methyl)but-2-enoate **2a** as the model substrate to examine the feasibility and reasonableness of this transformation. This reaction was executed under 50 °C, subjecting 1.0 equiv of iodobenzene diacetate **1a** to 1.0 equiv of **2a** in isopropanol (*i*-PrOH) for 1 h and the desired product **3a** was afforded in 20% yield (Table 1, entry 1). The treatment of **2a** with 1.2-1.8 equivalents of DIB yielded 12-35% of the product **3a**, and 1.4 equivalents of DIB was found to be the best (Table 1, entries 2-5). The different solvents such as ethanol, trifluoroethanol, acetonitrile (CH_3CN), toluene, dioxane and EGDME were screened and lower yields were obtained (Table 1, entries 6-11). Common alcohols with electron-donating group were more favorable than that with electron-withdrawing group (Table 1, entries 3 and 6 *vs.* entry 7). The chloroform promoted the reaction to give the product **3a** in 35% yield, which reaches the same level of reactivity as in isopropanol (Table 1, entry 12). Solvent screening studies revealed that DMF and DMSO are detrimental to the reaction (Table 1, entries 13 and 14). Therefore, we adopted chloroform with lower boiling point than isopropanol, readily to move, as solvent for futher optimization of reaction conditions. Fortunately, the structure of **3a** was confirmed oxazole through single-crystal X-ray diffraction analysis (Fig. 1).

Table 1. Optimization of reaction conditions.[a]



Entry	DIB (x equiv)	Solvent	Yield[b] (%)
1	1.0	*i*-PrOH	20
2	1.2	*i*-PrOH	33
3	1.4	*i*-PrOH	35
4	1.6	*i*-PrOH	27
5	1.8	*i*-PrOH	12
6	1.4	CH_3CH_2OH	28
7	1.4	CF_3CH_2OH	21
8	1.4	CH_3CN	10
9	1.4	Toluene	22
10	1.4	1,4-dioxane	24
11	1.4	EGDME	17
12	1.4	$CHCl_3$	35
13	1.4	DMF	trace
14	1.4	DMSO	N.R.[c]

[a] Conditions: **2a** (0.5 mmol) and DIB (specified) in solvent (1 mL) at 50 °C for 1 h. EGDME = ethylene glycol dimethyl ether, DMF = N,N-dimethylformamide, DMSO = Dimethyl sulfoxide.
[b] Isolated yields.
[c] N.R. = no reaction.

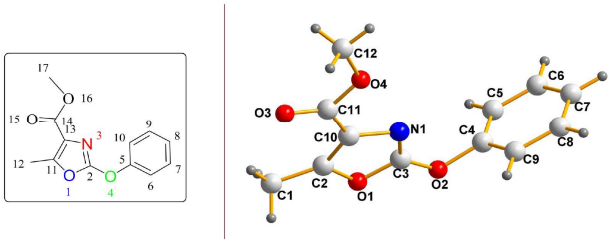
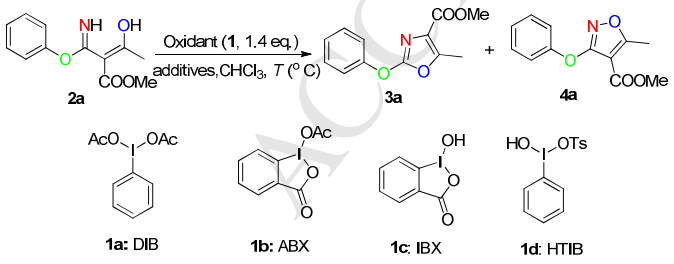


Fig. 1. X-ray single crystal structure of **3a**

The influences of different oxidants, temperatures, time and additives on the reaction were examined with the results shown in Table 2. Close to reaction at 50 °C (Table 2, entry 1), the reaction could occur at ambient temperature as well and the desired product **3a** was obtained in 31% yield (Table 2, entry 2). Temperature effect was significant to the reaction, and as a result, lowering the temperature to -20 °C, the yield was improved to 67%, whereas isoxazole **4a** became the major product (Table 2, entry 3). Further lowering the temperature to -30 °C, the reactivity dropped relatively (Table 2, entry 4). Oppositely, when the temperature was elevated to 80°C, the yield decreased sharply, and complex byproducts were observed (Table 2, entry 5). The effects of the reaction time were then examined and as a result, increasing reaction time to 2 h resulted in a slightly increase in 35% yield of **3a** (Table 2, entry 6 *vs.* entry 2); Shortening the reaction time to 0.5 h, 20 min and 10 min, the total yields were obtained of isomers **3a** and **4a** in 40%, 54% and 61%, respectively (Table 2, entries 7-9). With the reation time prolonged, the content of **3a** incresed significantly, and as a result, only oxazole **3a** was NMR-detected after 1 hour. With an attempt to improve the yield of oxazole **3a**, the different oxidants such as ABX (**1b**), IBX (**1c**) and HTIB (**1d**) were examined, and all of them were unsuccessful (Table 2, entries 10-12). To further improve the reactivity, several additives such as TEMPO, benzoylperoxide, AIBN, benzotriazol (BTA) were attempted (Table 2, entries 13-15), and as a result benzotriazol was most favorable to the reaction giving the oxazole **3a** in yield of 75% (for the detailed, see supporting information) (Table 2, entry 15). Accordingly, the optimal conditions were identified 1.4 equivalents of DIB reacted with 3-hydroxybut-2-enimidate in chloroform in the presence of 0.3 equivalent of BTA at room temperature for an hour.

Table 2. Evaluation of oxidants, temperature and time on the reaction.[a]

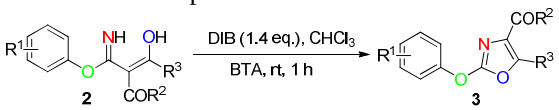


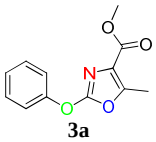
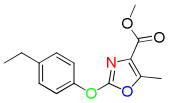
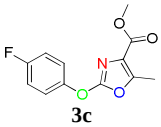
Entry	Oxidant (1.4 equiv)	*T* (°C)	Time (h)	Additives (equiv)	Yield[b] (%)	Ratio (**3a**/**4a**)[c]
1	**1a**	50	1	none	35	1/0
2	**1a**	rt	1	none	31	1/0
3	**1a**	-20	1	none	67	1/8
4	**1a**	-30	1	none	48	-[d]
5	**1a**	80	1	none	trace	-[d]
6	**1a**	rt	2	none	35	1/0
7	**1a**	rt	1/2	none	40	2.7/1
8	**1a**	rt	1/3	none	54	1/1.7
9	**1a**	rt	1/6	none	61	1/10.2
10	**1b**	rt	1	none	N.R.	-[d]
11	**1c**	rt	1	none	N.R.	-[d]
12	**1d**	rt	1	none	10	-[d]
13	**1a**	rt	1	TEMPO (0.2)	17	1/0
14	**1a**	rt	1	BTA (0.2)	66	1/0
15	**1a**	rt	1	BTA (0.3)	75	1/0

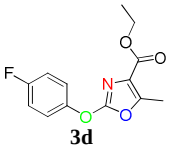
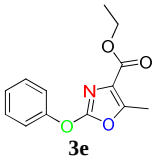
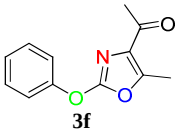
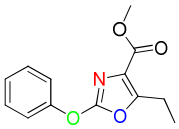
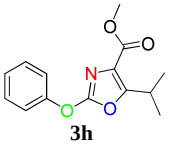
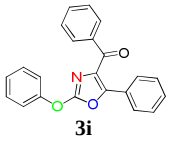
[a] Conditions: **2a** (0.5 mmol), oxidant (**1**, 1.4 eq.), $CHCl_3$ (1 mL), temperature (specified), time (specified). BTA = benzotriazol, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.
[b] Isolated yield.
[c] The molar ratio of **3a** and **4a** determined by ^{1}H NMR spectroscopy.
[d] Not detected the ratio of two isomers.

With the optimized conditions in hand, the scope of 3-hydroxybut-2-enimidate was investigated with the results shown in Table 3. Various substituted substrates were studied including methyl, ethyl, methoxy, ethoxy, fluoro, isopropyl and phenyl groups. We probed the effect of substitution on the benzene ring and the results showed that electron-withdrawing fluoro is more benificial than electron-donating group to the reaction (Table 3, entries 2-3). However, *m*-methoxy substituted benzene ring was not compatible with this reaction under standard conditions. Comparable to the methoxy on ester, ethyloxy group was found more active to the transformation in 60% yield in the absence of benzotriazol (Table 3, entry 4). Ethyloxy carbonyl and acetyl groups at 2-C were beneficial to the reaction (Table 3, entries 5-6). The effect of substitution R^3 at α-position of hydroxyl groups were also studied under the standard conditions and the results revealed that ethyl and isopropyl substituted substrates give yield in 54% and 60% in the absence of TBA, respectively (Table 3, entries 7 and 8). In particular, 3-hydroxybut-2-enimidate derivative with bulky phenyl groups also gave the desire product **3i** in yield of 60% (Table 3, entry 9).

Table 3. Substrate Scope.[a]



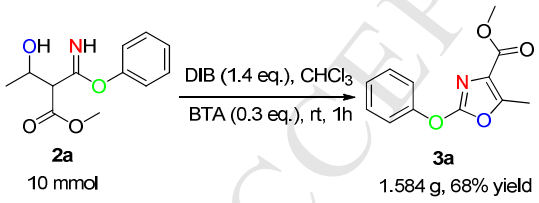
Entry	R^1	R^2	R^3	**3**	Yield[b] (%)
1	H	MeO	Me	 **3a**	75
2	*p*-Et	MeO	Me	 **3b**	41
3	*p*-F	MeO	Me	 **3c**	64

4	*p*-F	EtO	Me	 **3d**	60[c]
5	H	EtO	Me	 **3e**	70
6	H	Me	Me	 **3f**	68
7	H	MeO	Et	 **3g**	54[c]
8	H	MeO	*i*-Pr	 **3h**	60[c]
9	H	Ph	Ph	 **3i**	60

[a] Conditions: **2** (0.5 mmol), BTA (0.15 mmol) and DIB (0.7 mmol) in $CHCl_3$ (1 mL) at room temperature for 1 h.
[b] Isolated yield.
[c] without BTA

To demonstrate the practicability of our method, a large-scale experiment was conducted. Interestingly, methyl 5-methyl-2-phenoxyoxazole-4-carboxylate **3a** was obtained in yield of 68% when treating 10 mmol of 3-hydroxybut-2-enimidate **2a** under standard conditions (Scheme 2).

Scheme 2. Synthesis of oxazole **3a** in a large-scale.



In order to gain a better understanding of the mechanism, several control experiments were performed with the results shown in Fig. 2. The influence of reaction time on two isomers **3a** and **4a** was determined by the ratio of peak area and the chemical shift value of methyl group in NMR spectra. The ratio of **4a** and **3a** was 4.4:1 when the reaction proceeds for 5 minutes (I, Fig. 2). The NMR sample stood for 15 days in dark and the ratio of two structures remained the same basically (II, Fig. 2). Under the same circumstances, this tube continue to stand under visible light shinning for 54 days, and comparison of two methyl peak area integrals found that the ratio of **4a** and **3a** decreased significantly (III, Fig. 2). With the reaction time extended to 10 minutes, we discovered the yields increased and the ratio of **4a** and **3a** was elevated to 10.2:1 (IV, Fig. 2). Continue to prolong the reaction time to 20 and 30 minutes, respectively, the yield of **4a** declined, the ratio of **3a** rose gradually, and only oxazole **3a** existed after 1 hour. (Fig. 2, V and VI). On the basis of these results, we came to a conclusion that 3-hydroxybut-2-enimidates was oxidized to form isoxazole firstly, and then isoxazole decomposed completely to generate oxazole partially.

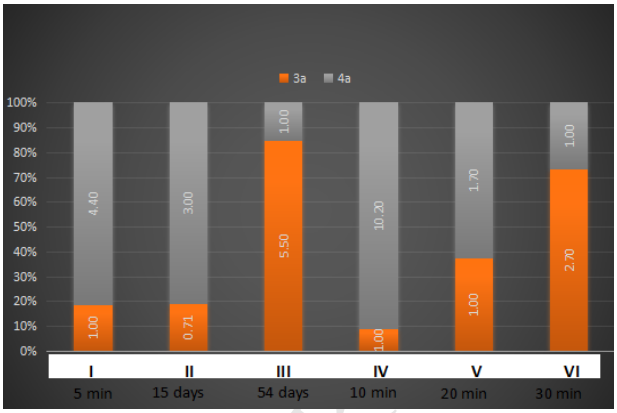


Fig. 2. Control experiments

Based on our experimental results, a plausible pathway was proposed to explain the oxidative rearrangement process of 3-hydroxybut-2-enimidate towards synthesis of oxazole as shown in Fig. 3.[13,19,20] The substrate would react with DIB to release an acetic acid and produce intermediate **A** with the formation of nitrogen-iodine bond. Followed by a nucleophilic attack of hydroxyl, cyclization takes place and affords an isoxazole **4**. There have two possible pathways from isoxazole to oxazole: i) with acetic acid generated continuously, isoxazole is protonated to form intermediate **B**. Through a σ-bond shift, three-membered ring intermediate **C** is formed, where a deprotonation gives rise to the free structure **D**. ii) alternatively, under the conditions of visible light shinning, the free radical intermediate **E** is generated from homolytic cleavage of nitrogen-oxygen bond and π-bond shift, which likewise reachs intermediate **D**. With the lone pair electron attack of nitrogen, three-membered ring is broken and a nitrile ylide **F** is formed. Followed by a nucleophilic attack of enol anion to nitril ylide, the desired cyclic oxazole **3** is finally assembled.

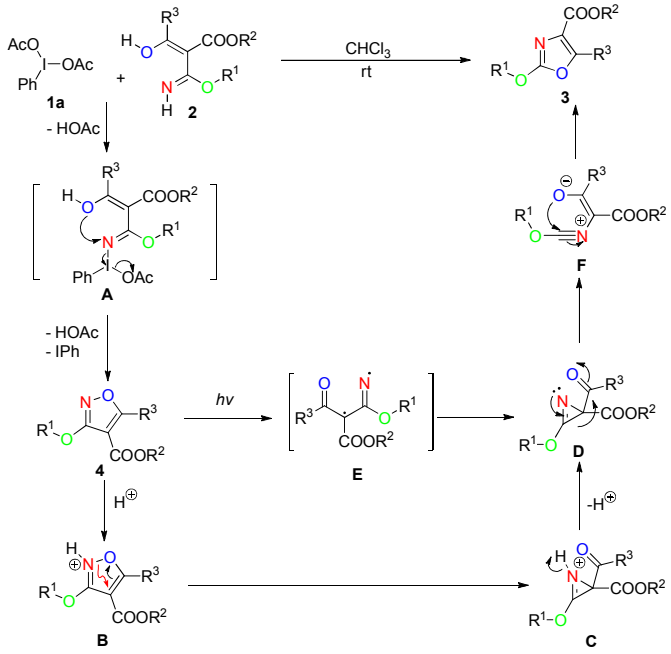


Fig. 3. Proposed reaction mechanism.

Conclusion

In conclusion, we have developed a direct oxidative rearrangement strategy to synthesize 2, 4, 5-trisubstituted oxazole by the use of hypervalent iodine reagent. A plausible mechanism has been accordingly proposed to interpret the observed reactivity.

Experimental section

4.1. General methods

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on 500 MHz spectrometer at 20-25°C. ^{1}H NMR spectra were reported in parts per million using tetramethylsilane TMS (δ = 0.00 ppm) as an internal standard. The data of ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants (*J*, Hz), and integration. ^{13}C NMR spectra were reported in parts per million using solvent $CDCl_3$ (δ = 77.2 ppm) as an internal standard. The data of ^{13}C NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), and coupling constants (*J*, Hz). Reactions were monitored by TLC and column chromatography was performed using silica gel. All the reagents used were of analytical grade, purchased from commercial suppliers and used without further purification unless otherwise specified.

4.2. General procedure for synthesis of 3-hydroxybut-2-enimidate (2a-i).[18]

Compound **2a-i** were synthesized according to the reported method: a mixture of ethyl acetoacetate (6 mmol), phenyl cyanate (5 mmol) in diethyl ether (10 mL) at room temperature for 40 hours. After completion of the reaction monitored by TLC, the volatile components were removed using a vacuum rotary evaporator. Purification by column chromatography on silica gel produced 3-hydroxybut-2-enimidates **2a-i**.

4.3. General procedure for synthesis of oxazole derivatives (3a-i).

Compound **3a-i** was synthesized by adding DIB (0.7 mmol) to 3-hydroxybut-2-enimidate (**2**, 0.5 mmol) in 1 mL of $CHCl_3$ at room temperature for 1 hour. After completion of the reaction, the reaction mixture was monitored by TLC, and the solvent was removed using a vacuum rotary evaporator. Purification by column chromatography on silica gel provided oxazoles **3**.

*4.2.1. Methyl-5-methyl-3-phenoxyisoxazole-4-carboxylate (**4a**).* Prepared from methyl-3-hydroxy-2-(imino(phenoxy)methyl)but-2-enoate; isolated as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48-7.44 (m, 4H), 7.33 (t, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.8, 167.2, 156.8, 153.6, 130.4, 127.1, 118.5, 53.3, 51.4, 28.5.

*4.2.2. Methyl-5-methyl-2-phenoxyoxazole-4-carboxylate (**3a**).* Prepared from methyl-3-hydroxy-2-(imino(phenoxy)methyl)but-2-enoate; isolated as colorless solid (36 mg, 31% yield). ^{1}H NMR (500MHz, $CDCl_3$): δ =7.41-7.38 (m, 2H), 7.34-7.33 (m, 2H), 7.25-7.22 (m, 1H), 3.86 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7, 157.7, 153.2, 152.2, 130.0, 126.5, 126.0, 119.5, 52.1, 12.0.

*4.2.3. Methyl-2-(4-ethylphenoxy)-5-methyloxazole-4-carboxylate (**3b**).* Prepared from methyl-2-((4-ethylphenoxy)(imino)methyl)-3-hydroxybut-2-enoate; isolated as colorless solid (47mg, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24-7.19 (m, 4H), 3.85 (s, 3H), 2.64 (q, *J* = 8 Hz, 2H), 2.58 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 158.1, 152.2, 151.2, 142.1, 129.3, 126.4, 119.4, 52.1, 28.4, 15.8, 12.0.

*4.2.4. Ethyl 2-(4-fluorophenoxy)-5-methyloxazole-4-carboxylate (**3c**).* Prepared from methyl-2-((4-fluorophenoxy)(imino) methyl)3-hydroxybut-2-enoate; isolated as colorless solid (38 mg, 30% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.31 (m, 2H), 7.10-7.07 (m, 2H), 3.86 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6, 161.3, 159.4, 152.3, 149.0, 126.4, 121.2 (d, *J* = 8.8Hz), 116.6 (d, *J* = 23.8Hz), 52.1, 12.0.

*4.2.5. Ethyl-2-(4-fluorophenoxy)-5-methyloxazole-4-carboxylate (**3d**).* Prepared from ethyl-2-((4-fluorophenoxy)(imino)methyl)-3-hydroxybut-2-enoate; isolated as colorless solid (80 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.32 (m, 2H), 7.10-7.06 (m, 2H), 4.34 (q, *J* = 7.0 Hz, 2H), 2.58 (s, 3H), 1.36 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3, 161.3, 159.3, 152.1, 149.0, 126.8, 121.2 (d, *J* = 8.8 Hz), 116.6 (d, *J* = 23.8 Hz), 61.2, 14.5, 12.1.

*4.2.6. Ethyl-5-methyl-2-phenoxyoxazole-4-carboxylate (**3e**).* Prepared from ethyl-3-hydroxy-2-(imino(phenoxy)methyl)but-2-enoate; isolated as liquid (47 mg, 38% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41-7.38 (m, 2H), 7.34-7.32 (m, 2H), 7.25-7.21 (m, 1H), 4.34 (q, *J* = 7.5 Hz, 2H), 2.58 (s, 3H); 1.36 (t, *J* = 7.5Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3, 157.6, 153.3, 152.0, 130.4, 120.0, 127.1, 126.0, 119.4, 118.5, 61.1, 14.5, 12.1.

*4.2.7 1-(5-methyl-2-phenoxyoxazol-4-yl)ethanone (**3f**).* Prepared from phenyl-2-acetyl-3-hydroxybut-2-enimidate; isolated as solid (59 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.27-7.24 (m, 1H), 2.58 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 156.8, 153.3, 150.1, 133.7, 130.0, 125.9, 119.3, 28.1, 12.2.

*4.2.8 Methyl-5-ethyl-2-phenoxyoxazole-4-carboxylate (**3g**).* Prepared from methyl-3-hydroxy-2 (imino(phenoxy)methyl)pent-2-enoate; isolated as liquid (67 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.38 (m, 2H), 7.35-7.33 (m, 2H), 7.25-7.22 (m, 1H), 3.86 (s, 3H), 3.03 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7,157.8, 157.2, 153.3, 130.0, 126.0, 125.5, 119.5, 52.1, 19.6, 12.3.

*4.2.9. Methyl-5-isopropyl-2-phenoxyoxazole-4-carboxylate (**3h**).* Prepared from methyl-3-hydroxy-2-(imino(phenoxy)methyl)-4-methylpent-2-enoate; isolated as solid (78 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (t, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 3.86 (s, 3H), 3.79-3.73 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7, 160.4, 157.7, 153.2, 130.0, 126.0, 124.4, 119.4, 52.1, 26.1, 20.8.

*4.2.10. (2-phenoxy-5-phenyloxazol-4-yl)(phenyl)methanone (**3i**).* Prepared from phenyl-2-benzoyl-3-hydroxy-3-phenylacrylimidate; isolated as colorless solid (92 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09-8.07 (m, 2H), 7.94-7.93 (m, 2H), 7.55-7.52 (m, 1H), 7.46-7.39 (m, 9H), 7.28-7.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.4, 157.4, 153.4, 150.7, 137.4, 133.2, 132.9, 130.5, 130.2, 130.0, 128.7, 128.3, 127.7, 127.1, 126.1, 119.3.

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Supplementary Material

Supplementary data (^{1}H & ^{13}C NMR spectra of the compounds) associated with this article can be found in the online version, at

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