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SCOPE AND LIMITATIONS OF A MODIFIED HANTZSCH REACTION FOR THE SYNTHESIS OF OXAZOLE-DEHYDROAMINO ACID DERIVATIVES FROM DEHYDROAMINO ACID AMIDES

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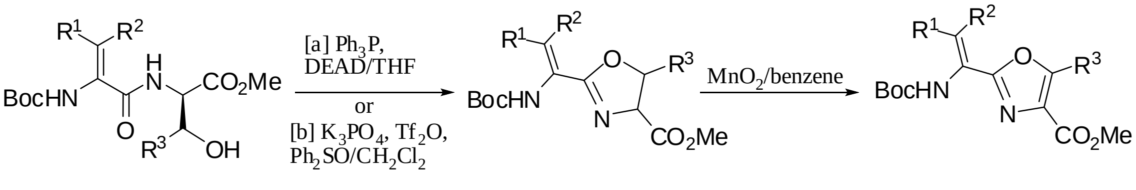
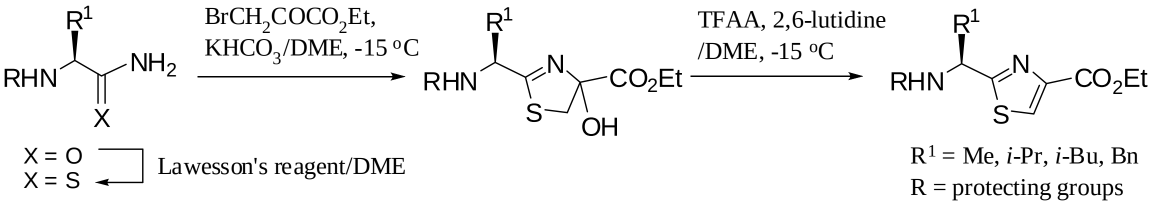
Abstract – A variety of oxazole derivatives that possess an α,β-unsaturated substituent at the 2-position were conveniently synthesized in good yields via a Hantzsch-type reaction between dehydroamino acid amides and β-bromopyruvate derivatives. Furthermore, oxazoles with substituents at the 2- and 5-positions were also obtained in good yields using the corresponding β-substituted β-bromopyruvate derivatives. A revised reaction mechanism to explain the enhanced reactivity of dehydroamino acid amides for the Hantzsch-oxazole-type reaction is presented.

INTRODUCTION

The synthesis of oxazole–containing bioactive natural products[1] has been an important subject over the last two decades. Among the various synthetic routes for the oxazole ring system that have been reported,[2-4] a popular strategy involves the heterocyclization of a serine or threonine side chain onto a dehydroamino acid amide carbonyl group to give an oxazoline that is subsequently oxidized to the oxazole (Scheme 1). Alternatively, thiazole building blocks of natural products can be conveniently synthesized via a modified Hantzsch reaction of thioamides that are derived from α- amino acids with β-halopyruvate (Scheme 2).[5]



Scheme 1. Synthesis of oxazole fragments of the berninamycins, A10255[4a,b]



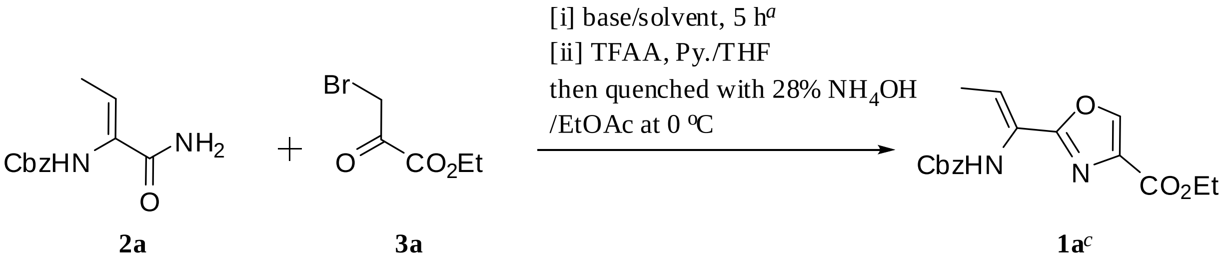
Scheme 2. The modified Hantzsch thiazole synthesis[5e-g]

However, the application of such conditions on the corresponding acid amides derived from saturated α-amino acids only gave the desired oxazole derivatives in moderate yields.[4a,b] The differences in the reactivities are presumably due to the nucleophilic properties of oxygen and sulfur. Therefore, we decided to develop a general synthetic methodology for preparing oxazole building blocks via Hantzsch-type reactions of acid amide derivatives that possess conjugated carbonyl oxygens with enhanced nucleophilicity. In 1996, Panek and co-workers reported on the efficient reaction of cinnamic acid amide with ethyl β-bromopyruvate to give the corresponding oxazole derivative,[6a] which was further converted to the tris-oxazole derivative in high yield.[6b] A similar type of oxazole synthesis based on the Hantzsch thiazole synthesis was reported by Bagley[7] and Hoffman.[8] Unfortunately, the enhanced reactivities and limitations of this special case of the Hantzsch protocol were not discussed. Herein, we describe the scope and limitations of the Hantzsch-oxazole protocol for synthesizing 2,4- and 2,4,5-substituted oxazole derivatives (having a dehydroamino substituent at the 2-position) from dehydroamino acid amide derivatives obtained from *N*-protected dehydroamino acids[9] and methyl or ethyl β-bromopyruvate derivatives (with or without a β-substituent).

RESULTS AND DISCUSSION

We initially examined the reaction conditions for the Hantzsch-type reaction between a dehydroamino acid amide (**2a**)[9] and ethyl β-bromopyruvate (**3a**)[10] towards the synthesis of oxazole **1a**. Favorable results were obtained with moderate temperatures and the use of a mild inorganic base. As shown in Table 1, optimal reaction conditions involved THF under reflux with $NaHCO_3$ as a base (entry 5). Reactions with $NaHCO_3$ and K_2CO_3 at room temperature did not proceed (entry 3 and 4). Furthermore, under homogeneous conditions (entries 1 and 2), **3a** rapidly decomposed, even at rt, such that the reaction did not occur. Reactions at higher or lower temperatures, or in the presence of an organic base (homogeneous conditions) were not fruitful. In contrast, **2a** was relatively stable at higher temperatures. Our results strongly indicated that both the reaction rate and the decomposition rate of **3a** required careful consideration.

Table 1. Hantzsch-type reaction conditions between a dehydroamino acid amide (**2a**) and ethyl bromopyruvate (**3a**)

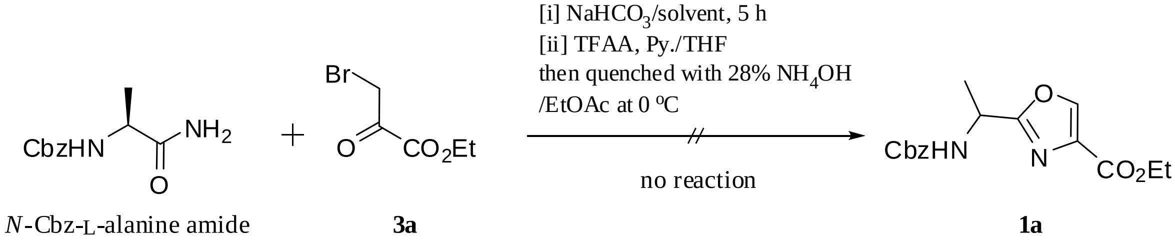


entry	base	solvent	temperature	yield [%][b]
1	pyridine	THF	rt	no reaction
2	Et_3N	THF	rt	no reaction
3	K_2CO_3	THF	rt	no reaction
4	$NaHCO_3$	THF	rt	no reaction
5	$KHCO_3$	THF	reflux (66 °C)	49
6	$NaHCO_3$	THF	reflux (66 °C)	85
7	$NaHCO_3$	toluene	70 °C	73
8	$NaHCO_3$	toluene	reflux (111 °C)	50
9	$NaHCO_3$	MeCN	reflux (82 °C)	70

[a] The reaction was carried out using **2a** (0.8 mmol), **3a** (2 equiv), and base (5 equiv) in solvent (5 mL).
[b] Isolated yield of **1a**.
[c]The geometric configuration of **1a** was deduced from the reaction mechanistic studies using **4e** and **4f** in Scheme 4.

Consequently, the optimal reaction conditions shown in entry 5, Table 1 were employed to explore the scope and limitations of the reaction between **3a** and various β-substituted dehydroamino acid amides (derivatives of **2a**) (Table 2). The reactions were allowed to proceed until the disappearance of substrates **2** (as determined by TLC) to maximize the yields of **1**. In some cases, due to the instability of **3a** (see above), extra portions of **3a** (2 equiv) were added after 5 and 10 h. Longer reaction times (over 5 h) were required in many cases, which can be attributed to the steric hindrance between the bulky substituents of the substrates **2** and β-bromopyruvate derivative **3**, with the exception of entry 6. Interestingly, the reactivities of the methoxy (entry 6, enhanced reactivity) and nitro (entry 7, reduced reactivity) derivatives, compared to that of entry 5 in Table 1. These results may suggested that the reaction rate decrease with the increasing electron-withdrawing effect of substituents R_1 (or/and R_2) such as NO_2, CO_2Me on the dehydroamino acid amide. (Relative reaction rate for substituents: Me > Ph; Me >

CH_2CO_2Me; *p*-MeO-Ph > Ph > *p*-NO_2-Ph). Futhermore, this Hantzsch-type reaction of *N*-Cbz-L-alanine amide[11] did not proceed (Scheme 3). Therefore, the conjugated double bond seems to play an important role in our Hantzsch-type reaction. Overall, oxazole-dehydroamino acid derivatives **1a-i** were conveniently synthesized in good yields via the Hantzsch-type reaction, but with careful attention to the conditions. As shown in Table 2, satisfactory yields and reaction times were observed for entries 1, 2, and 6.

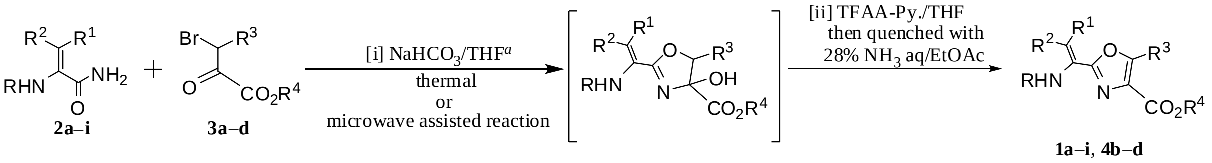


Scheme 3. The Hantzsch-type reaction of *N*-Cbz-L-alanine amide

Subsequently, the Hantzsch-type reaction was applied towards the synthesis of a 5-substituted oxazole backbone, which is found in various natural products. As shown in Table 2, we first investigated the synthesis of 5-substituted oxazole dehydroamino acid derivatives using methyl β-substituted β-bromopyruvates (**3b-d**), which were readily prepared from the dehydroamino acids.[12] Methyl β-substituted β-bromopyruvates **3b-d** were reacted with dehydroamino acid amide **2a** to give the corresponding oxazole derivatives in moderate yields. The influence of steric hindrance in the S_N2 reactions was evident from the long reaction times required for **3b** (entry 10) and **3c** (entry 11). In contrast to the unsubstituted substrate, the methyl β-substituted β-bromopyruvates were relatively stable. In the case of entry 12, the faster reaction rate can be explained by the enhanced S_N2 reaction at the benzylic position of **3d**. It is generally known that S_N2 reactions of halogenated substrates that involve either an allyl or benzyl group at the reaction center are enhanced by the stable $\pi-\pi$ conjugation between the sp^2 transition state and the π-electrons of the double bond. To improve the speed of the oxazole formation, these reactions were repeated under microwave irradiation at reflux conditions using a microwave apparatus.[13,14] As shown in Table 2, improved yields and reaction times were obtained in all cases under such conditions.

Newly proposed reaction mechanisms are shown in Scheme 3 to explain the enhanced reactivities of the Hantzsch-type reactions towards oxazole synthesis. The mechanism with the resonance contributor [**A**] is inferred from Babadjamian and co-workers' report[15] for the modified Hantzsch reaction of saturated amino thioacid amide derivatives to give the corresponding thiazole derivatives. An alternate mechanism with the consideration of resonance contributor [**B**], which involves stabilized resonance hybrid oxyanion intermediates, might support the enhanced reactivities.

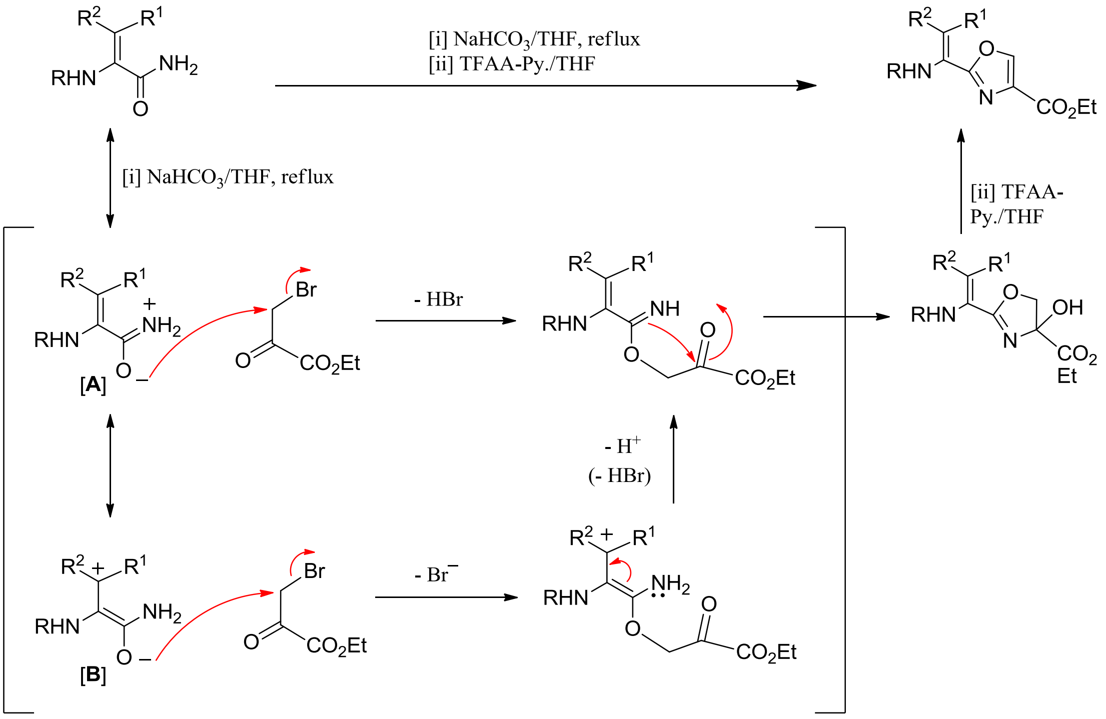
Table 2. Hantzsch-type reaction of various dehydroamino acid amides (**2a-i**) with ethyl β-bromopyruvate (**3a**) and its β-substituted derivatives (**3b-d**)



entry	2a–i			3a–d		products[i]	thermal reaction			microwave assisted reaction[g]		
	R	R¹	R²	R³	R⁴		**3** [equiv]	time [h][d]	yield [%][e]	**3** [equiv]	time [h][d]	yield [%][e]
1	**2a**: Cbz	H	Me	**3a**: H	Et	**1a**	2	5	85	2+2[f]	1	85
2	**2b**: Boc	H	Me			**1b**	2	5	83	2+2[f]	1	88
3	**2c**: Cbz	Me	Me			**1c**	2+2[b]	8	85	2+2+2[f]	1.5	84
4	**2d**: Cbz	H	*i*-Pr			**1d**	2+2[b]	8	88	2+2+2[f]	1.5	84
5	**2e**: Cbz	H	Ph			**1e**	2+2[b]	9	88	2+2+2[f]	1.5	88
6	**2f**: Cbz	H	*p*-MeOPh			**1f**	2	4	89	2+2[f]	1	84
7	**2g**: Cbz	H	*p*-NO_2Ph			**1g**	2+2+2[b]	14	87	2+2+2+2[f]	3	87
8	**2h**: Cbz	H	CH_2CO_2Me			**1h**	2+2[b]	9	69	2+2+2[f]	2	66
9	**2i**: Cbz	H	C_2H_4NHCbz			**1i**	2+2[b]	7	86	2+2+2[f]	1.5	91
10	**2a**: Cbz	H	Me	**3b**: Me	Me	**4b**	2+2[c]	22	74	2+2+2[f]	5	71
11				**3c**: *i*-Pr	Me	**4c**	2+2+2[c]	72	62	—	—	ND[h]
12				**3d**: Ph	Me	**4d**	2	7	78	2+2[f]	2.5	80

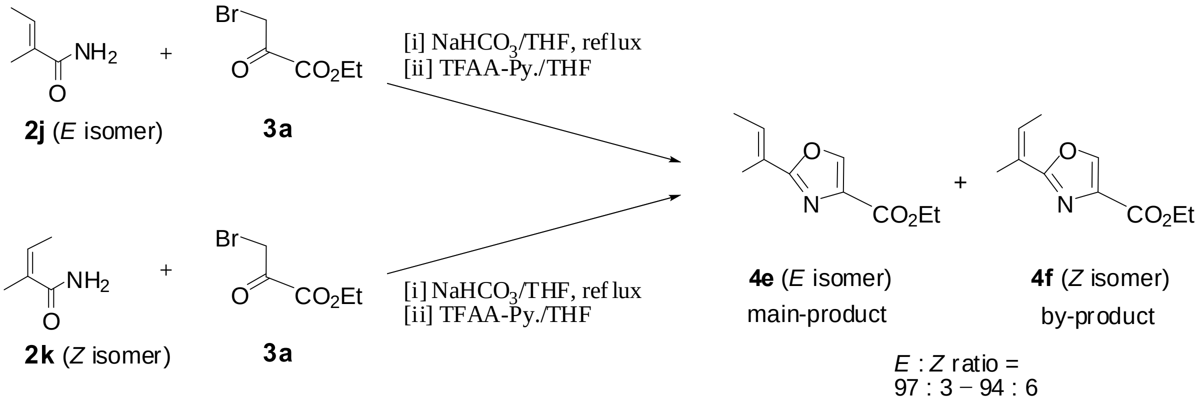
[a] A mixture of **2a-i** (0.8 mmol), **3a** (2 equiv), and base (5 equiv) was stirred in THF (5 mL) at reflux conditions.
[b] Additional portions (2 equiv) of **3a** were added after 5 h and 10 h.
[c] Additional portions (2 equiv) of **3b-d** were added after 12 h and 36 h.
[d] Time until the disapperance of **2** on TLC.
[e] Isolated yield of **1** and **4**.
[f] Additional portions (2 equiv) of **3** were added after 20 min, 1 h, and 2 h.
[g] Reflux conditions (100 W max initial MW power).
[h] Not determined (The resulting product was unstable under these conditions.).
[i] The geometric configurations of **1a-i** and **4b-d** were deduced from the reaction mechanistic studies using **4e** and **4f** in Scheme 4.

The reaction mechanism was further investigated using configurational isomers, as shown in Scheme 4. Because of the difficulty of preparing both (*E*)- and (*Z*)-isomers of the dehydroamino esters, the (*E*)- and (*Z*)-isomers of the α,β-unsaturated acid amides [2-methylbutenamide (**2j** and **2k**)][16] were synthesized first as model compounds in good yields from the corresponding commercially available (*E*)- and (*Z*)-acids by treatment with DCC (*N*,*N*-dicyclohexylcarbodiimide) and HOSu (*N*-hydroxysuccinimide) in aqueous NH_3 solution. These olefins apparently do not undergo isomerization because the corresponding products were exclusively obtained.[16] To prepare such substrates **2a-i**, three established methods, such as (1) β-elimination (*anti*-elimination) of Ser, Thr, and Cys,[9] (2) condensation of α-ketoester and protected amine ($CbzNH_2$),[9,17] (3) Wittig reaction of *N*-protected diethylphospholylglycine ester to the corresponding aldehyde, and subsequent amidation,[9,17] were employed. It is known that these reactions predominantly give (*Z*)-dehydroamino esters. The preference for the (*Z*)-isomer may be attributed to the thermodynamic stability of the configuration by a similar isomerization mechanism *via* the sp^2 carbocation resonance contributor [**B**] as shown in Scheme 4. If the subsequent Hantzsch-type reaction proceeds with the resonance contributor [**A**] without participation of resonance contributor [**B**], the configuration of R_1 and R_2 (*E*, *Z*) will be retained in the products (**4e** and **4f**),[18] whereas if the reaction proceeds *via* resonance contributor [**B**], the configuration will be influenced (scrambled) by the sp^2 intermediate to give the thermodynamically stable products. Our results show that both starting isomers afforded oxazole products with similar ratios between the (*E*)- and (*Z*)-isomers. In other words, the reaction proceeded *via* resonance contributor [**B**] with isomerization. The configurations of **4e** and **4f** were determined using NMR experiments (^{1}H and NOESY) and the results were compared to reported spectral data.[18] Other possibilities still remain, for example, that isomerization occurs via Michael addition – elimination reactions of oxazolines or oxazoles. However this mechanism cannot explain the enhanced reactivities.



Scheme 4. Proposed reaction mechanisms of the Hantzsch-type reactions

Although the configurations of the oxazole-dehydroamino acid derivative products **1a-i** have yet to be established by NMR and X-ray structure analyses, because of the absence of critical NOE correlations and the difficulties in getting single crystals, the stable configurations of the starting dehydroamino esters may be retained by deducing from the reaction mechanistic study using **4e** and **4f** (Scheme 5). The preference for the (*Z*)-isomer may also be in good agreement with the thermodynamically stable configuration of the corresponding starting dehydroamino ester by the mechanism *via* resonance contributor [**B**].



Scheme 5. Further investigation of the reaction mechanism using (*E*)- and (*Z*)-isomers of the α,β-unsaturated acid amides [2-methylbutenamides (**2j** and **2k**)]

In conclusion, various oxazole-dehydroamino acid derivatives were efficiently synthesized from β-bromopyruvates and dehydroamino acid amides (easily derived from the corresponding dehydroamino acids) via a Hantzsch-type reaction with microwave irradiation. Using β-substituted β-bromopyruvates, this methodology was applied towards the synthesis of various 5-substituted oxazole derivatives, which can be found in the structures of various natural products.[4d,19] Additional investigations indicated that the reaction mechanism of our Hantzsch-type reaction, due to the contribution of the α,β-unsaturated bond on the dehydroamino moiety, might differ from that of the modified Hantzsch reaction in thiazole synthesis. Because the synthesized oxazole-dehydroamino ester intermediate itself can serve as an activated substrate, it is our belief that this Hantzsch-type oxazole synthetic methodology can contribute towards the synthesis of various natural products that possess substituted mono-, bis-, and tris-oxazole moieties.

EXPERIMENTAL

All melting points were measured using a Yanaco Model MP-J3 micro-melting point apparatus, and are uncorrected. IR spectra were recorded using a Jasco FT/IR-4200 spectrometer in KBr. ^{1}H NMR spectra were recorded on spectrometers operating at 500 MHz and 600 MHz in chloroform-*d* or dimethylsulfoxide-d_6 referenced to tetramethylsilane (0.00 ppm). ^{13}C NMR spectra were recorded on spectrometers operating at 125 MHz and 150 MHz in chloroform-*d* or dimethylsulfoxide-d_6. The assignments of various NMR spectra were assisted by homonuclear ($^1H/^1H$) correlation spectroscopy (COSY), nuclear Overhuser and exchange spectroscopy (NOESY), nuclear Overhauser effect (NOE), and/or heteronuclear ($^1H/^{13}C$) correlation spectroscopy (HETCOR) experiments. The chemical shifts, coupling constants, and IR frequencies were recorded in δ, Hz, and cm^{-1} units, respectively. Column chromatography was performed on silica gel (Silica gel 60, 70-230 mesh; Silica gel 60N, spherical, neutral, 70-230 mesh). Thin-layer chromatography (TLC) on Silica gel $60F_{254}$ was used to monitor the reactions and to certify the purity of the reaction products by heating after spraying with ninhydrin-ethanol solution, phosphomolybdic acid ethanol-H_2SO_4 solution, and cerium ammonium molybdate water-H_2SO_4 solution.

Microwave Irradiation Experiments. All microwave experiments were performed with the Wave Magic® (EYELA MWO-1000S). Experiments were carried out in standard microwave process with Pyrex flask. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times). Reaction temperature was measured using a teflon-coated thermocouple of type K.

General procedure for the reaction of dehydroamino acid amides (2a-i) and ethyl β-bromopyruvate (3a)

Thermal reaction: To a stirred solution of compound **2a-i** (0.8 mmol) in THF (5 mL) were added $NaHCO_3$ (336 mg, 5 equiv) and a solution of ethyl β-bromopyruvate (**3a**) (312 mg, 2 equiv) at 0 °C. After stirring for 5-11 h at reflux, the resulting solution was diluted with $CHCl_3$ (10 mL) and organic layer was washed with brine and water (10 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give a yellow syrup as crude oxazoline. Crude oxazoline was dissolved in THF (5 mL), TFAA (trifluoroacetic anhydride) (333 μL, 3 equiv) and pyridine (388 μL, 6 equiv) were added to the above THF solution with stirring at 0 °C for 30 min. After the disappearance of oxazoline on TLC, the reaction mixture was concentrated *in vacuo* to give a brown syrup. Resulting residue was further dissolved in EtOAc (5 mL), 28% NH_4OH (1 mL) was added to the mixture and stirred at 0 °C for 15 min. The reaction mixture was poured into brine, washed with water, brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give oxazole-dehydroamino acid derivatives **1a-i** (69-89%), which were purified on a silica gel column with hexanes-EtOAc.

Microwave assisted reaction: To a stirred solution of **2a-i** (0.8 mmol) in THF (5 mL) were added $NaHCO_3$ (336 mg, 5 equiv) and a solution of ethyl β-bromopyruvate (**3a**) (312 mg, 2 equiv) in THF (1 mL) at 0 °C. The flask was flushed with argon, heated with stirring at reflux under microwave irradiation for 5-72 min. After cooling to rt, the reaction mixture was diluted with $CHCl_3$ (10 mL) and the organic layer was washed with brine and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a yellow syrup. Resulting syrup was dissolved in THF (5 mL), TFAA (333 μL, 3 equiv) and pyridine (388 μL, 6 equiv) were added to the mixture at 0 °C, and stirred for 30 min. The reaction mixture was concentrated *in vacuo* to give brown syrup. Resulting syrup was further dissolved in EtOAc (5 mL), 28% NH_4OH (1 mL) was added to the above mixture at 0 °C, and stirred for 15 min. Reaction mixture was poured into brine, washed with brine and water, dried over anhydrous $MgSO_4$, concentrated *in vacuo*. Resulting brown syrup was purified on a silica gel column to give 5-substituted oxazole derivatives **1a-i** (66-91%).

Ethyl (*Z*)-2-[1-((1-(Benzyloxy)carbonyl)amino)prop-1-en-1-yl]oxazole-4-carboxylate (Cbz-ΔAbu-Ozl-OEt) (1a): Yield 85%; white solid; mp 95-97 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3302, 2959, 1732, 1505, 1313 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz, Et's C*H*$_3$), 1.67 (3H, d, *J* = 7.2 Hz, ΔAbu's C*H*$_3$), 4.39 (2H, q, *J* = 7.2 Hz, Et's C*H*$_2$), 5.16 (2H, s, Cbz's C*H*$_2$), 6.48 (1H, br s, N*H*), 6.62 (1H, q, *J* = 7.2 Hz, vinyl's *H*), 7.33-7.39 (5H, m, Cbz's Ph*H*), 8.12 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 61.3, 67.5, 67.5, 122.8, 128.2, 128.3, 128.5, 134.1, 135.9, 143.7, 153.9, 160.5, 161.1. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{18}N_2NaO_5$ 353.1113, found 353.1095. Anal. Calcd for $C_{17}H_{18}N_2O_5$ (330.12): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.74; H, 5.30; N, 8.21.

Ethyl (*Z*)-2-[1-(((*tert*-Butoxy)carbonyl)amino)prop-1-en-1-yl]oxazole-4-carboxylate (Boc-ΔAbu-Ozl-OEt) (1b): Yield 83%; white solid; mp 130.5-132 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3322, 2980, 1724, 1498, 1317 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.38 (3H, t, *J* = 7.1 00Hz, Et's C*H*$_3$), 1.47 (9H, s, Boc's *t*-Bu), 1.87 (3H, d, *J* = 7.2 Hz, ΔAbu's C*H*$_3$), 4.39 (2H, q, *J* = 7.1 Hz, Et's C*H*$_2$), 6.26 (1H, br s, N*H*), 6.55 (1H, q, *J* = 7.2 Hz, vinyl's *H*), 8.14 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 14.2, 28.1, 61.3, 80.6, 123.0, 127.1, 134.0, 143.5, 152.9, 160.8, 161.2. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{20}N_2NaO_5$ 319.1270, found 319.1256. Anal. Calcd for $C_{14}H_{20}N_2O_5$ (296.14): C, 56.75; H, 6.80; N, 9.45. Found: C, 56.71; H, 6.58; N, 9.29.

Ethyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)-2-methylprop-1-en-1-yl]oxazole-4-carboxylate (Cbz-ΔVal-Ozl-OEt) (1c): Yield 85%; white solid; mp 108-109 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3160, 2981, 1733, 1506, 1317 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-*d*$_6$ at 60 °C) δ 1.29 (3H, t, *J* = 7.1 Hz, Et's C*H*$_3$), 1.86, 2.10 (3H × 2, each s, ΔVal's C*H*$_3$ × 2), 4.29 (2H, q, *J* = 7.1 Hz, Et's C*H*$_2$), 5.05 (2H, s, Cbz's C*H*$_2$), 7.31-7.36 (5H, m, Cbz's Ph*H*), 8.66 (1H, bs, N*H*), 8.80 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, DMSO-*d*$_6$, 60 °C) δ 13.9, 20.4, 20.7, 60.2, 65.5, 117.5, 127.3, 127.5, 128.0, 132.7, 136.6, 138.8, 143.7, 154.3, 159.9, 160.4. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{20}N_2NaO_5$ 367.1270, found 367.1251. Anal. Calcd for $C_{18}H_{20}N_2O_5$ (344.14): C, 62.78; H, 5.85; N, 8.13. Found: C, 62.44; H, 5.47; N, 7.84.

Ethyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)-2,3-dimethylbut-1-en-1-yl]oxazole-4-carboxylate (Cbz-ΔLue-Ozl-OEt) (1d): Yield 88%; yellow syrup; IR (KBr, neat) ν_{max} 3305, 2962, 1730, 1500, 1320 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.08 (6H, d, *J* = 6.6 Hz, ΔLeu's CH_3), 1.38 (3H, t, *J* = 7.2 Hz, Et's CH_3), 2.78 (1H, dqq, *J* = 10.2, 6.6, 6.6 Hz, ΔLeu's *H*), 4.39 (2H, q, *J* = 7.2 Hz, Et's CH_3), 5.15 (2H, s, Cbz's CH_2), 6.27 (1H, bs, N*H*), 6.39 (1H, d, *J* = 10.2 Hz, vinyl's *H*), 7.26-7.36 (5H, m, Cbz's Ph*H*), 8.11 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.7, 22.3, 27.9, 61.7, 67.9, 120.4, 128.6, 128.6, 128.9, 134.6, 136.3, 141.3, 144.0, 155.0, 161.1, 161.6. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{22}N_2NaO_5$ 381.1426, found 381.1395.

Ethyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)-2-phenylethen-1-yl]oxazole-4-carboxylate (Cbz-ΔPhe-Ozl-OEt) (1e): Yield 88%; colorless amorphous; IR (KBr, disk) ν_{max} 3254, 2980, 1733, 1506, 1317 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.39 (3H, t, *J* = 7.2 Hz, Et's CH_3), 4.40 (2H, q, *J* = 7.2 Hz, Et's CH_2), 5.11 (2H, s, Cbz's CH_2), 6.68 (1H, s, N*H*), 7.29 (1H, s, vinyl's *H*), 7.29-7.53 (10H, m, Cbz's Ph*H*, ΔPhe's Ph*H*), 8.16 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.3, 61.4, 67.6, 120.9, 128.0, 128.2, 128.2, 128.5, 128.7, 129.1, 129.4, 133.8, 134.5, 135.8, 143.9, 153.8, 160.9, 161.1. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{22}H_{20}N_2NaO_5$ 415.1270, found 415.1279.

Ethyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)-2-(4-methoxyphenyl)vinyl]oxazole-4-carboxylate (Cbz-ΔTyr(OMe)-Ozl-OEt) (1f): Yield 89%; colorless amorphous; IR (KBr, disk) ν_{max} 3291, 2981, 1728, 1511, 1318 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-*d*$_6$ at 80 °C) δ 1.31 (3H, t, *J* = 7.1 Hz, Et's CH_3), 3.80 (3H, s, Tyr's OMe), 4.32 (2H, q, *J* = 7.1 Hz, Et's CH_2), 5.10 (2H, br s, Cbz's CH_2), 6.94-7.66 (10H, m, Cbz's Ph*H* , ΔTyr's Ph*H*, Vinyl's *H*), 8.73 (1H, s, ring-*H*), 9.17 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-*d*$_6$ at 80°C) δ 13.7, 55.0, 60.2, 65.6, 113.8, 119.6, 126.0, 127.1, 127.4, 127.9, 128.9, 131.0, 133.4, 136.4, 144.5, 154.1, 159.7, 160.3, 161.1. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{23}H_{22}N_2NaO_6$ 445.1376, found 445.1353.

Ethyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)-2-(4-nitrophenyl)vinyl]oxazole-4-carboxylate (Cbz-*p*-NO$_2$ΔPhe-Ozl-OEt) (1g): Yield 87%; yellow solid; mp 162-164 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3255, 3150, 1724, 1704, 1521, 1347, 1108, 738 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.39 (3H, t, *J* = 7.2 Hz, Et's CH_3), 4.41 (2H, q, *J* = 7.2 Hz, Et's CH_2), 5.06 (2H, s, Cbz's CH_2), 7.20 (1H, br s, N*H*), 7.24 (1H, s, vinyl's *H*), 7.33 (5H, br s, Cbz's Ph*H*), 7.59 (2H, d, *J* = 8.6 Hz, Ph*H*), 8.09 (2H, d, *J* = 8.6 Hz, Ph*H*), 8.22 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.3, 61.6, 67.9, 123.2, 123.5, 123.7, 128.5, 128.5, 128.6, 129.6, 134.8, 135.5, 141.0, 144.5, 147.0, 152.9, 160.0, 160.7. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{22}H_{19}N_3NaO_7$ 460.1120, found 460.1150. Anal. Calcd for $C_{22}H_{19}N_3O_7$ (437.12): C, 60.41; H, 4.38; N, 9.61; O, 25.60. Found: C, 60.34; H, 4.34; N, 9.51.

Ethyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)-4-methoxy-4-oxobut-1-en-1-yl]oxazole-4-carboxylate (Cbz-ΔGlu(OMe)-Ozl-OEt) (1h): Yield 69%; colorless syrup; IR (KBr, neat) ν_{max} 3307, 2954, 1733, 1508 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.38 (3H, t, *J* = 7.1 Hz, Et's C*H*$_3$), 3.37 (2H, d, *J* = 7.2 Hz, γ-*H*), 3.73 (3H, s, COOC*H*$_3$), 4.39 (2H, q, *J* = 7.2 Hz, Et's C*H*$_2$), 5.16 (2H, s, Cbz's C*H*$_2$), 6.67 (1H, t, *J* = 7.2 Hz, vinyl's *H*), 6.79 (1H, br s, N*H*), 7.32-7.42 (5H, m, Cbz's Ph*H*), 8.15 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.3, 33.7, 52.2, 61.4, 67.8, 122.1, 123.9, 128.3, 128.4, 128.6, 134.2, 135.6, 144.1, 153.6, 159.7, 161.0, 170.1. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{20}N_2NaO_7$ 411.1168, found 411.1128.

Ethyl (*Z*)-2-[[1,4-Bis(((benzyloxy)carbonyl)amino)]but-1-en-1-yl]oxazole-4-carboxylate (Cbz-ΔOrn(*N*Cbz)-Ozl-OEt) (1i): Yield 91%; colorless syrup; IR (KBr, neat) ν_{max} 3320, 2981, 1719, 1525, 1249 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.37 (3H, t, *J* = 7.1 Hz, Et's C*H*$_3$), 2.51 (2H, dt, *J* = 6.4, 7.4 Hz, ΔOrn's γ-C*H*$_2$), 3.39 (2H, dt, *J* = 4.8, 6.4 Hz, ΔOrn's δ-C*H*$_2$), 4.38 (2H, q, *J* = 7.1 Hz, Et's C*H*$_2$), 5.09, 5.14 (4H, each s, Cbz's C*H*$_2$ × 2), 5.32 (1H, br s, N*H*), 6.46 (1H, t, *J* = 7.4 Hz, vinyl's *H*), 6.66 (1H, br s, N*H*), 7.28-7.36 (10H, m, Cbz's Ph*H* × 2), 8.12 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.3, 28.6, 39.8, 61.4, 66.6, 67.7, 123.5, 128.0, 128.0, 128.3, 128.4, 128.5, 128.6, 129.1, 134.2, 135.7, 136.6, 143.9, 154.2, 156.5, 160.0, 161.0. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{26}H_{27}N_3NaO_7$ 516.1747, found 516.1720.

General procedure for the preparation of dehydroamino acid amides (**2a-i**). To a solution of *N*-protected dehydroamino acid (ΔAA-OH) (4.0 mmol) in THF (10 mL) was added a solution of DCC (1.1 equiv) in THF at 0 °C. After stirring for 30 min, HOSu (*N*-hydroxysuccinimide) (1.1 equiv) was added to the resulting mixture. After stirring at room temperature for 5 min, the precipitates (dicyclohexylurea: DCU) was filtrated off through a pad of Celite. The filtrate was concentrated *in vacuo* to give a residue. The resulting residue was dissolved in EtOAc (10 mL), added 28% NH_4OH (1 mL), and stirred continuously for 30 min at room temperature. The reaction mixture was washed with brine water, dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give a *N*-protected ΔAA-NH_2 (**2a-i**)(70-92%), which was recrystallized from acetone-hexanes.

(*Z*)-2-((Benzyloxy)carbonyl)amino-2-butenamide (Cbz-ΔAbu-NH$_2$) (2a): Yield 82%; white solid; mp 109-110 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3468, 3144, 1692, 1657, 1503 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 1.62 (3H, d, *J* = 7.0 Hz, ΔAbu's C*H*$_3$), 5.05 (2H, s, Cbz's C*H*$_2$), 6.23 (1H, q, *J* = 7.0 Hz, vinyl's *H*), 7.01 (1H, s, NH$_2$'s *H*), 7.31–7.38 (6H, m, Cbz's Ph*H*, N*H*$_2$), 8.50 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 12.9, 65.7, 126.0, 127.7, 127.8, 128.3, 131.4, 136.8, 154.1, 166.4. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{12}H_{14}N_2NaO_3$ 257.0902, found 257.0882. Anal. Calcd for $C_{12}H_{14}N_2O_3$ (234.10): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.47; H, 6.02; N, 11.70.

(*Z*)-2-((*tert*-Butoxy)carbonyl)amino-2-butenamide (Boc-ΔAbu-NH_2) (2b): Yield 86%; white solid; mp 116-117 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3293, 2979, 1677, 1647 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.39 (9H, s, Boc's *t*-Bu), 1.59 (3H, d, J = 6.9 Hz, ΔAbu's CH_3), 6.11 (1H, br s, N*H*), 6.95, 7.20 (2H, each s, NH_2), 8.00 (1H, br s, vinyl's *H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 12.9, 28.1, 78.5, 125.0, 131.7, 153.3, 166.8. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_9H_{16}N_2NaO_3$ 2223.1058, found 2223.1081. Anal. Calcd for $C_9H_{16}N_2O_3$ (200.24): C, 53.98; H, 8.05; N, 13.99. Found: C, 53.63; H, 8.42; N, 13.70.

2-((Benzyloxy)carbonyl)amino-3-methyl-2-butenamide (Cbz-ΔVal-NH_2) (2c): Yield 87%; white solid; mp 146-148 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3451, 2903, 1667, 1641, 1599 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.66, 1.92 (3H × 2, each s, ΔVal's CH_3 × 2), 5.04 (2H, s, Cbz's CH_2), 7.01, 7.11 (1H × 2, each s, NH_2), 7.31-7.38 (5H, m, Cbz's Ph*H*); 8.48 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.4, 20.7, 65.5, 125.6, 127.7, 127.8, 128.3, 133.6, 137.0, 154.3, 167.3. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{13}H_{16}N_2NaO_3$ 271.1059, found 271.1030.

(*Z*)-2-((Benzyloxy)carbonyl)amino-4-methyl-2-pentenamide (Cbz-ΔLue-NH_2) (2d): Yield 92%; white solid; mp 117-118 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3278, 2961, 1684, 1507 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.94 (6H, d, J = 6.4 Hz, ΔLeu's CH_3), 2.56 (1H, m, ΔLeu's *H*), 5.04 (2H, s, Cbz's CH_2), 6.02 (1H, d, J = 6.9 Hz, vinyl's *H*), 7.01 (1H, s, NH_2), 7.30-7.38 (6H, m, Cbz's Ph*H*, NH_2), 8.49 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 21.8, 26.2, 65.6, 127.6, 127.8, 128.2, 128.3, 136.9, 138.5, 154.6, 166.6. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{14}H_{18}N_2NaO_3$ 285.1215, found 285.1256.

(*Z*)-2-((Benzyloxy)carbonyl)amino-3-phenyl-2-propenamide (Cbz-ΔPhe-NH_2) (2e): Yield 87%; white solid; mp 166-167 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3337, 1713, 1607 cm^{-1}; ^{1}H NMR (500MHz, DMSO-d_6) δ 5.06 (2H, s, Cbz's CH_2), 7.06 (1H, s, vinyl's *H*), 7.23 (2H, s, NH_2), 7.30-7.56 (10H, m, Cbz's Ph*H*, ΔPhe's Ph*H*), 7.59 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 65.7, 127.5, 127.7, 127.9, 128.3, 128.4, 128.5, 129.4, 129.5, 134.2, 136.9, 154.4, 167.0. HRMS (ESI-TOF) *m/z* : [M+Na]$^+$ calcd for $C_{17}H_{16}N_2NaO_3$ 319.1059, found 319.1044.

(*Z*)-2-((Benzyloxy)carbonyl)amino-3-(4-methoxyphenyl)-2-propenamide (Cbz-*p*-ΔTyr(OMe)-NH_2) (2f): Yield 77%; white solid; mp 147-149 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3452, 3336, 3208, 3105, 2898, 1720, 1662, 1578 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (3H, s, Tyr's OMe), 5.20 (2H, s, Cbz's CH_2), 5.66 (2H, br s, NH_2), 6.89 (2H, d, J = 8.7 Hz, Tyr's Ph*H*), 7.27 (1H, s, vinyl's *H*), 7.27-7.37 (5H, m, Cbz's Ph*H*), 7.44 (2H, d, J = 8.7 Hz, Tyr's Ph*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.9, 25.6, 34.0, 55.3, 67.8, 114.3, 125.8, 128.3, 128.4, 128.6, 131.3, 131.3, 135.8, 160.4, 167.6; ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.4, 55.2, 65.7, 113.9, 126.6, 127.2, 127.6, 127.7, 128.3, 128.5, 131.2, 137.0, 154.4, 159.5, 167.2. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{18}N_2NaO_4$ 349.1164, found: 349.1134.

(*Z*)-2-((Benzyloxy)carbonyl)amino-3-(4-nitrophenyl)-2-propenamide (Cbz-*p*-NO$_2$ΔPhe-NH$_2$) (2g): Yield 82%; yellow solid; mp 182-184 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3294, 3466, 3245, 3145, 1688, 1522, 1342, 1255 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-*d$_6$*) δ 5.06 (2H, s, Cbz's C*H$_2$*), 7.01 (1H, s, vinyl's *H*) 7.32-7.40 (6H, m, Cbz's Ph*H*, N*H$_2$*'s *H*), 7.75 (2H, d, *J* = 8.8 Hz, Tyr's Ph*H*), 7.78 (1H, s, N*H$_2$*'s *H*), 8.18 (2H, d, *J* = 8.8 Hz, Tyr's Ph*H*); 9.18 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-*d$_6$*) δ 66.0, 123.5, 123.7, 127.7, 127.8, 128.3, 130.1, 133.0, 136.6, 141.4, 146.4, 154.0, 166.8; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{15}N_3NaO_5$ 364.0909, found 364.0946.

Methyl (*Z*)-5-Amino-4-[((benzyloxy)carbonyl)amino]-5-oxo-3-pentenoate (Cbz-ΔGlu(OMe)-NH$_2$) (2h): Yield 70%; white solid; mp 110-111 °C; IR (KBr, disk) ν_{max} 3435, 3388, 3191, 2997, 1725, 1701, 1670, 1655, 1609, 1278 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-*d$_6$*) δ 3.18 (2H, d, *J* = 7.0 Hz, γ-H), 3.61 (3H, s, COOC*H$_3$*), 5.05 (2H, s, Cbz's C*H$_2$*), 6.21 (1H, t, *J* = 7.0 Hz, vinyl's *H*), 7.14 (1H, s, N*H$_2$*), 7.32-7.38 (5H, m, Cbz's Ph*H*), 7.48 (1H, s, N*H$_2$*), 8.70 (1H, s, CbzN*H*); ^{13}C NMR (150 MHz, DMSO-*d$_6$*) δ 32.2, 51.7, 65.9, 121.4, 127.7, 127.8, 128.3, 132.3, 136.7, 153.9, 165.9, 170.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{16}N_2NaO_5$ 315.0956, found 315.1022. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.29): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.52; H, 5.52; N, 9.75.

(*Z*)-2,5-Di[((benzyloxy)carbonyl)amino]-2-pentenamide (Cbz-ΔOrn(*N*Cbz)-NH$_2$) (2i): Yield: 71%; white solid; mp 128-130 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3296, 3036, 1686, 1509, 1249 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-*d$_6$*) δ 2.21 (2H, dd, *J* = 6.9, 13.5 Hz, γ-*H*), 3.08 (2H, dd, *J* = 6.6, 13.5 Hz, δ-*H*), 5.01, 5.04 (2H × 2, each s, Cbz's C*H$_2$*), 6.09 (1H, t, *J* = 6.9 Hz, vinyl's *H*), 7.06 (1H, s, N*H$_2$*), 7.29-7.37 (12H, m, Cbz's Ph*H* × 2, NH$_2$'s *H*, N*H*), 8.57 (1H, s, N*H*); ^{13}C NMR (150 MHz, DMSO-*d$_6$*) δ 27.6, 39.3, 65.2, 65.7, 127.3, 127.6, 127.7, 127.7, 127.7, 127.8, 128.3, 128.3, 131.5, 136.8, 137.2, 154.2, 156.1, 166.4. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{23}N_3NaO_5$ 420.1535, found 420.1537.

(*E*)-2-Methyl-2-butenamide (2j) (Tiglic acid amide): The preparation procedure was the same as **2a-i**. Yield 81 %; white solid; mp 126.5-127.5 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3376, 3181, 2921, 1666, 1612 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.87 (3H, dq, *J* = 1.5, 7.1 Hz, γ-C*H$_3$*), 1.91 (3H, dq, *J* = 1.5, 1.5 Hz, C*H$_3$*), 5.63 (1H, s, NH$_2$'s *H*), 5.71 (1H, br qq, *J* = 1.5, 7.1 Hz, vinyl's *H*), 6.30 (1H, s, NH$_2$'s *H*).

(*Z*)-2-Methyl-2-butenamide (2k) (Angelic acid amide): The preparation procedure was the same as **2a-i**. Yield 88 %; white solid; mp 164.5-166.5 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3344, 3178, 2935, 1676, 1597 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.77 (3H, dq, *J* = 1.2, 6.9 Hz, γ-C*H$_3$*), 1.85 (3H, dq, *J* = 1.2, 1.2 Hz, C*H$_3$*), 5.88, 6.22 (1H × 2, each s, NH$_2$'s *H* × 2), 6.52 (1H, br qq, *J* = 1.2, 6.9 Hz, vinyl's *H*).

Methyl 3-Bromo-2-oxobutanoate (3b). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.82 (3H, d, J = 6.8 Hz, $CHBrCH_3$), 3.94 (3H, s, OCH_3), 5.17 (1H, q, J = 6.8 Hz, C*H*Br). This compound was used in the next step without further purification after usual workup, because this compound was unstable.

Methyl 3-Bromo-2-oxo-4-methylpentanoate (3c): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06, 1.14 (3H × 2, each d, J = 6.6 Hz, $(CH_3)_2CH$), 2.36 (1H, dq, J = 7.9, 6.6 Hz, $(CH_3)_2CH$), 3.93 (3H, s, OCH_3), 4.85 (1H, d, C*H*Br, J = 7.9 Hz). This compound was used in the next step without further purification after usual workup, because this compound was unstable.

Methyl 3-Bromo-2-oxo-3-phenylpropanoate (3d): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.94 (3H, s, OCH_3), 6.21 (1H, s, C*H*Br), 7.38-7.47 (5H, m, Ph*H*). This compound was used in the next step without further purification after usual workup, because this compound was unstable.

General procedure for the reaction of dehydroamino acid amides (2a) and β-substituted β-bromopyruvate (3b-d).

Conventional heating: To a stirred solution of **2a** (0.8 mmol) in THF (5 mL) were added $NaHCO_3$ (336 mg, 5 equiv) and a solution of methyl β-substituted β-bromopyruvate (**3b-d**) (2 equiv) in THF (1 mL) at 0 °C. After stirring for 5-72 h at reflux, the resulting solution was diluted with $CHCl_3$ (10 mL) and the organic layer was washed with brine and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a yellow syrup. Resulting syrup was dissolved in THF (5 mL), TFAA (trifluoracetic anhydride) (333 μL, 3 equiv) and pyridine (388 μL, 6 equiv) were added to the mixture at 0 °C, and stirred for 30 min. The reaction mixture was concentrated *in vacuo* to give brown syrup. Resulting syrup was further dissolved in EtOAc (5 mL), 28% NH_4OH (1 mL) was added to the above mixture at 0 °C, and stirred for 15 min. reaction mixture was poured into brine, washed with brine and water, dried over anhydrous $MgSO_4$, concentrated *in vacuo*. Resulting brown syrup was purified on a silica gel column to give 5-substituted oxazole derivatives (**4b-d**) (62-78%).

Microwave heating: To a stirred solution of **2a** (0.8 mmol) in THF (5 mL) were added $NaHCO_3$ (336 mg, 5 equiv) and a solution of methyl β-substituted β-bromopyruvate (**3b-d**) (2 equiv) in THF (1 mL) at 0 °C. The flask was flushed with argon, heated with stirring at reflux under microwave irradiation for 5-72 min. After cooling to rt, the reaction mixture was diluted with $CHCl_3$ (10 mL) and the organic layer was washed with brine and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a yellow syrup. Resulting syrup was dissolved in THF (5 mL), TFAA (trifluoracetic anhydride) (333 μL, 3 equiv) and pyridine (388 μL, 6 equiv) were added to the mixture at 0 °C, and stirred for 30 min. The reaction mixture was concentrated *in vacuo* to give brown syrup. Resulting syrup was further dissolved in EtOAc (5 mL), 28% NH_4OH (1 mL) was added to the above mixture at 0 °C, and stirred for 15 min. reaction mixture was poured into brine, washed with brine and water, dried over anhydrous $MgSO_4$, concentrated *in vacuo*. Resulting brown syrup was purified on a silica gel column to give 5-substituted oxazole derivatives (**4b-d**)(71-80%).

Methyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)prop-1-en-1-yl]-5-methyloxazole-4-carboxylate (Cbz-ΔAbu-MeOzl-OMe) (4b): Yield 74%; colorless crystals; mp 136-138 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3307, 2953, 1717, 1507 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.85 (3H, d, *J* = 7.2 Hz, ΔAbu's CH_3), 2.60 (3H, s, ring-CH_3), 3.90 (3H, s, OCH_3), 5.15 (2H, s, Cbz's CH_2), 6.45 (1H, br s, N*H*), 6.54 (1H, q, *J* = 7.2 Hz, vinyl's *H*), 7.32-7.37 (5H, m, Cbz's Ph*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 12.1, 14.0, 52.0, 67.4, 122.8, 127.4, 128.0, 128.2, 128.2, 128.5, 136.0, 153.9, 156.5, 157.8, 162.6. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{17}H_{18}N_2NaO_5$ 353.1113, found 353.1118.

Methyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)prop-1-en-1-yl]-5-isopropyloxazole-4-carboxylate (Cbz-ΔAbu-*i*-PrOzl-OMe) (4c): Yield 62%; yellow amorphous; IR (KBr, disk) ν_{max} 3567, 2979, 1717, 1507 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.28 (6H, d, *J* = 7.0 Hz, *i*-Pr's CH_3 × 2), 1.87 (3H, d, *J* = 7.2 Hz, ΔAbu's CH_3), 3.76 (1H, dq, *J* = 7.0, 7.0 Hz, *i*-Pr's C*H*), 3.90 (3H, s, COOCH_3), 5.16 (2H, s, Cbz's CH_2), 6.51 (1H, br s, N*H*), 6.55 (1H, q, *J* = 7.2 Hz, vinyl's *H*), 7.32-7.39 (5H, m, Cbz's Ph*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.0, 20.6, 26.1, 52.0, 67.4, 122.9, 126.1, 127.3, 128.2, 128.2, 128.5, 136.0, 153.9, 157.5, 162.6, 164.6. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{22}N_2NaO_5$ 381.1426, found: 381.1401.

Methyl (*Z*)-2-[1-(((Benzyloxy)carbonyl)amino)prop-1-en-1-yl]-5-phenyloxazole-4-carboxylate (Cbz-ΔAbu-PhOzl-OMe) (4d): Yield 80%; coloeless needles; mp 148.5-151 °C (acetone-hexanes); IR (KBr, disk) ν_{max} 3301, 2955, 1724, 1493 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.90 (3H, d, *J* = 7.2 Hz, ΔAbu's CH_3), 3.93 (3H, s, OCH_3), 5.18 (2H, s, Cbz's CH_2), 6.49 (1H, br s, N*H*), 6.68 (1H, d, *J* = 7.3 Hz, vinyl's *H*), 7.26-7.48 and 8.00-8.02 (10H, m, Cbz's Ph*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.1, 52.2, 52.3, 67.5, 122.8, 126.7, 127.4, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 130.3, 130.5, 135.9, 153.9, 155.4, 157.8, 162.4. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{22}H_{20}N_2NaO_5$ 415.1270, found 415.1251.

Reaction of 2-methylbutenamide (2j, k) and ethyl β-bromopyruvate (3a). To a solution of **2j** (**2k**), (80 mg, 0.8 mmol) in THF (5 mL) were added NaHCO$_3$ (336 mg, 5 equiv) and ethyl β-bromopyruvate (**3a**) (312 mg, 2 equiv) at 0 °C, and stirred for 2 h at reflux conditions. After cooling to room temperature, the reaction mixture was diluted with CHCl$_3$ (10 mL), washed with water (10 mL) and brine (10 mL), dried over anhydrous MgSO$_4$ and concentrated *in vacuo* to give a yellow syrup. Remaining residue was dissolved in THF (5mL), TFAA (178 μL, 3 equiv) and pyridine (390 μL, 6 equiv) were added to the mixture at 0 °C, and stirred for 30 min. the reaction mixture was concentrated *in vacuo* to give a brown syrup. The resulting syrup was further dissolved in EtOAc (5 mL), 28% NH$_4$OH (1 mL) was added to the mixture at 0 °C. After stirring for 15 min, the reaction mixture was washed with brine and dried over anhydrous MgSO$_4$, concentrated *in vacuo* to give **4e** and **4f**, which were purified on a silica gel column with hexanes-EtOAc (1:1 v/v).

Ethyl (*E*)-2-(1-Methyl-1-propen-1-yl)-4-oxazolecarboxylate (4e) (*main product*): Yield 88%; colorless syrup; IR (KBr, neat) ν_{max} 3469, 3157, 2983, 2930, 2858, 1742, 1719, 1576, 1541, 1317 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.39 (3H, t, *J* = 7.1 Hz, Et's CH_3), 1.87 (3H, dq, *J* = 7.2, 1.1 Hz, γ-CH_3), 2.10 (3H, dq, *J* = 1.1, 1.1 Hz, CH_3), 4.39 (2H, q, *J* = 7.1 Hz, Et's CH_2), 6.73 (1H, qq, *J* = 1.1, 7.2 Hz, vinyl's *H*), 8.12 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 12.7, 14.1, 14.3, 61.1, 123.9, 131.1, 134.1, 143.0, 161.6, 164.4. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{10}H_{13}NNaO_3$ 218.0793, found 218.0748.

NOE correlation: γ-CH_3 ⟵⟶ CH_3, γ-CH_3 ⟵no observation⟶ vinyl's H

Ethyl (*Z*)-2-(1-Methyl-1-propen-1-yl)-4-oxazolecarboxylate (4f) (*by-product*): Yield 5%; colorless syrup; IR (KBr, neat) ν_{max} 3448, 3157, 2981, 2923, 2852, 1742, 1720, 1575, 1151, 1113 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.39 (3H, t, *J* = 7.1 Hz, Et's CH_3), 2.11 (3H, dq, *J* = 7.3, 1.5 Hz, γ-CH_3), 2.15 (3H, dq, *J* = 1.5, 1.5 Hz, CH_3), 4.40 (2H, q, *J* = 7.1 Hz, Et's CH_2), 6.04 (1H, qq, *J* = 1.5, 7.3 Hz, vinyl's *H*), 8.19 (1H, s, ring-*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.3, 15.7, 21.2, 61.1, 122.6, 133.2, 133.8, 142.7, 161.6, 163.5. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{10}H_{13}NNaO_3$ 218.0793, found 218.0748.

NOE correlation: γ-CH_3 ⟵no observation⟶ CH_3, γ-CH_3 ⟵⟶ vinyl's *H*

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