One-Pot Preparation of Oxazol-5(4*H*)-ones from Amino Acids in Aqueous Solvents

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A method for one-pot synthesis of oxazol-5(4*H*)-ones has been developed using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), which is available for the activation of carboxylic acids in an aqueous solvent. The oxazolones were prepared by the *N*-acylation of amino acids with carboxylic acids and the subsequent cyclodehydration of the resulting *N*-acylamino acids by the addition of *N*,*N*-diethylaniline. Since both these reactions proceed effectively with the same coupling reagent, DMT-MM, in aqueous solvents, the procedure is simplified and becomes easy to perform. In addition, 5-(triazinyloxy)oxazole derivatives have been synthesized by controlling the basicity of the reaction system.

Key words oxazolone; oxazole; dehydrocondensation; cyclodehydration; aqueous solvent

Oxazol-5(4*H*)-ones (henceforth referred to as oxazolones) are useful precursors for the synthesis of substituted heterocyclic compounds,[1] natural products,[2] and chiral amino acids.[3,4] In general, the preparation of oxazolones from amino acids is effected by two-step synthesis: *N*-acylation of the amino group followed by cyclodehydration involving the activation of the carboxy group. The *N*-acylation of amino acids can be carried out in an aqueous solvent, typically using Schotten–Baumann conditions,[5] while the cyclodehydration of the resulting *N*-acylamino acids to form oxazolones is performed under anhydrous conditions with dehydrating reagents, such as carbodiimides and acid anhydrides. Thus, these reactions must be performed in separate vessels. If the latter reaction occurs in an aqueous solvent, both reactions can be conducted in the same vessel using water-soluble amino acids as a starting compound. Therefore, the procedure for preparing oxazolones becomes simplified. In this study, we focused on 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM)[6] as a dehydrocondensing reagent because the chemoselective activation of carboxy groups using DMT-MM efficiently proceeds even in an aqueous solvent.[7] We report here a one-pot method for the synthesis of oxazolones from amino acids. In this method, DMT-MM is utilized successfully for both the *N*-acylation of amino acids with carboxylic acids and the subsequent cyclodehydration of the resulting *N*-acylamino acids.[8,9]

Results and Discussion

To find the optimum reaction conditions for the one-pot method, we first examined each reaction separately using L-leucine (**2a**) as a model compound.[10,11] After several attempts, we succeeded in finding the optimum reaction conditions for the first reaction. Benzoic acid (**1**) was treated with DMT-MM in the presence of *N*-methylmorpholine (NMM) in acetone–H_2O (3 : 1) at room temperature for 15 min; then an aqueous solution of **2a** and NaOH was added (Chart 1). As a result, *N*-benzoyl-L-leucine (**3a**) was obtained in a satisfactory yield (91%). The addition of NaOH as a base was found to be essential to complete the coupling reaction.

The second reaction needs to follow the final conditions of the former reaction to achieve a one-pot reaction. Thus, at first **3a** was treated with DMT-MM in acetone–H_2O (1 : 1) at room temperature in the presence of NMM (1.0 eq), which is generated in the first reaction (Chart 2). Unfortunately, the desired 4-isobutyl-2-phenyl-oxazol-5(4*H*)-one (**4a**) was produced in only 28% yield, along with the generation of 4-isobutyl-2-phenyl-5-(4,6-dimethoxy-1,3,5-triazin-2-yloxy)oxazole (**5a**) in 33% yield as a by-product, which was probably formed by the base-catalyzed coupling between DMT-MM and **4a** (Table 1, Entry 1). When the reaction was conducted in the absence of NMM, **4a** was formed in a low yield (4%) with the recovery of **3a** (96%), and **5a** was not formed at all, indicating that a base is essential for the completion of cyclodehydration.[12–15]

On the basis of the assumption that the yield of oxazole derivative **5a** could be decreased by the separation of relatively lipophilic **4a** from water-soluble DMT-MM, we conducted the reaction in a biphasic solvent system composed of CH_2Cl_2–acetone–H_2O (1 : 1 : 1). As a result, the yield of **5a** decreased

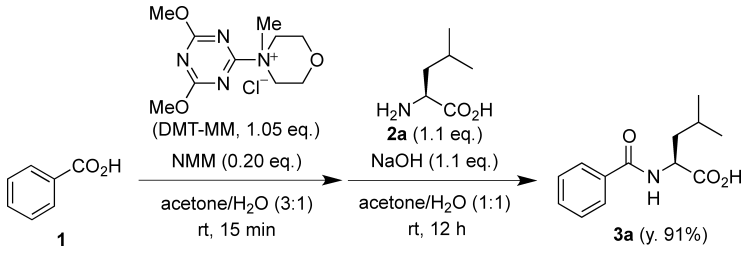

Chart 1. *N*-Benzoylation of L-Leucine (**2a**) in Acetone/H_2O

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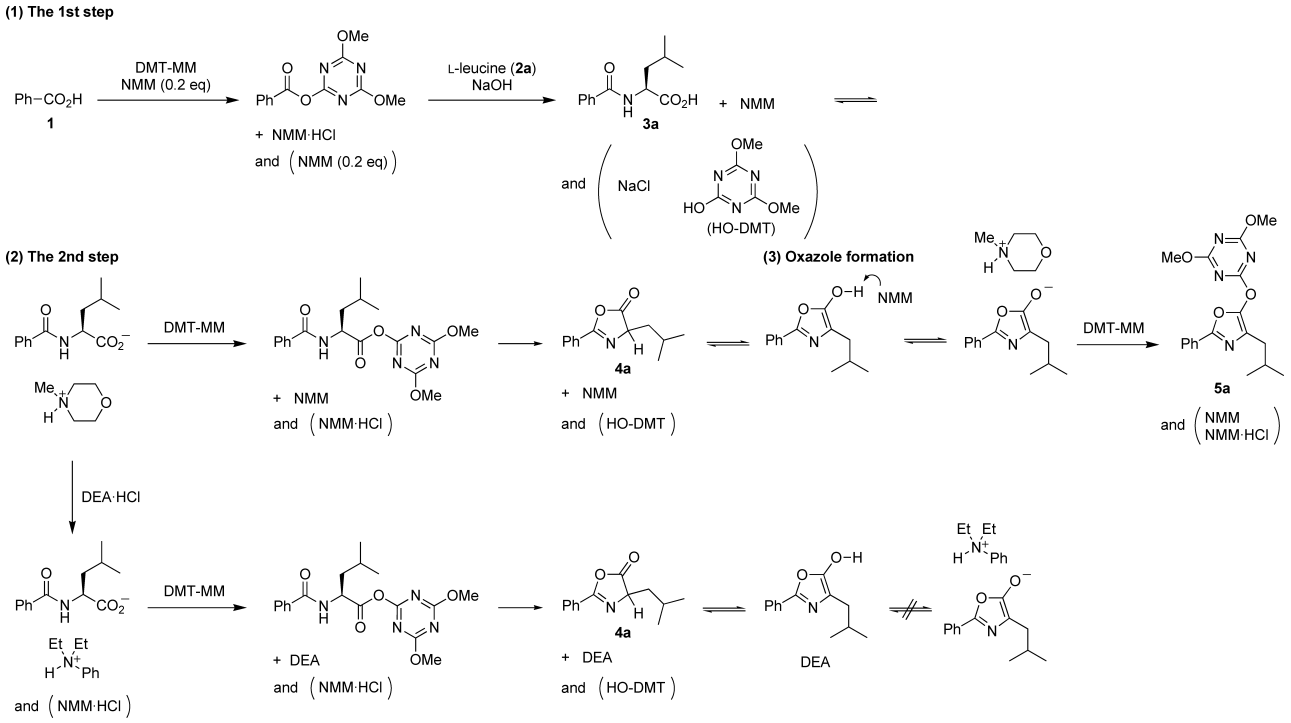


The reaction products in the parentheses are eliminated from the following reaction balances.

Chart 2. Reaction Balances for the Reactants and the Products in Every Step of the Reactions

to 15%, and the desired **4a** was obtained in 68% yield (Entry 2). Furthermore, the yield of **4a** increased and that of **5a** decreased by employing organic bases weaker than NMM (pK_a=7.41).[16–19] The best result was obtained with *N*,*N*-diethylaniline (DEA; pK_a=6.56) giving **4a** in 78% and **5a** in 1% yields (Entry 4). Interestingly, the reaction was not improved by the use of an inorganic base, $NaHCO_3$, despite having the lowest pK_a value (6.37) among the bases examined (Entry 5). Compared with yields in the biphasic solvent system, when the reaction using DEA was performed in the monophasic solvent of acetone–H_2O (1 : 1), the yield of **4a** decreased slightly and that of **5a** increased slightly (Entry 4 *vs.* 6). Consequently, we employed the reaction conditions of Entry 4 for the second reaction, where DEA was used as a base in the biphasic CH_2Cl_2–acetone–H_2O (1 : 1 : 1).

Next, we attempted to prepare oxazolone **4a** directly from amino acid **2a** by utilizing the one-pot method under the optimum reaction conditions described above. After the completion of the *N*-acylation of **2a** (rt, 4.5 h), CH_2Cl_2 and DEA hydrochloride (DEA·HCl, 1.3 eq) were added to the reaction mixture. Then, the second reaction was started by the addition of DMT-MM (1.1 eq) to the resulting biphasic mixture. The desired **4a** was obtained in 71% yield along with a small amount of **5a** (2% yield). As illustrated in Chart 2, the addition of DEA·HCl was intended to recreate the conditions corresponding to those of Table 1, Entry 4, by replacing the *N*-methylmorpholinium ion, which is the counter cation of the carboxylate anion of **3a**, with the *N*,*N*-diethylanilinium ion. In addition, the free NMM that arises from the reaction of DMT-MM and the carboxylate anion of **3a** can be converted into NMM·HCl by the liberation of the free DEA. The resulting NMM·HCl can no longer act as a base to deprotonate from **4a**.

We succeeded in preparing various oxazolones **4** from amino acids under the described optimum conditions. As shown in Table 2, oxazolones (**4a**–**4f**) with a lipophilic substituent

Table 1. Cyclodehydration of **3a** under Various Conditions

Entry	Base (pK_a)	Solvent	Reaction time (h)	Yield of **4a**[a] (%)	Yield of **5a**[a] (%)
1	NMM (7.41)[16]	Acetone–H_2O (1 : 1)	2	28	33
2	NMM (7.41)[16]	CH_2Cl_2–acetone–H_2O (1 : 1 : 1)[b]	5	68	15
3	2,6-Lutidine (6.96)[17]	CH_2Cl_2–acetone–H_2O (1 : 1 : 1)[b]	5	77	8
4	DEA (6.56)[18]	CH_2Cl_2–acetone–H_2O (1 : 1 : 1)[b]	5	78	1
5	$NaHCO_3$ (6.37)[19]	CH_2Cl_2–acetone–H_2O (1 : 1 : 1)[b]	5	66	16
6	DEA (6.56)[18]	Acetone–H_2O (1 : 1)	2	71	6

a) The yields were determined by ^{1}H-NMR using (*E*)-*N*,*N*-dimethylcinnamamide as an internal standard. *b*) Biphasic solvent system.

at the 4-position (R^2) were obtained in fairly good yields (71–79%, Entries 1–6). On the other hand, reactions of relatively high water-soluble alanine and glycine were found to afford low yields (**4g**: 37%, **4i**: 35%; Entries 7 and 10). The yield of **4g** was improved to 54% by shortening the reaction time in the second reaction (Entry 7 *vs.* 8). The yield of **4i** increased moderately by the use of 2.5 eq of DMT-MM coupled with a lesser reaction time (Entry 10 *vs.* 11). In addition, the yield of 4-methyloxazolone (**4g**) was improved by replacing the 2-phenyl group with a more lipophilic 1-naphthyl group (**4h**, Entry 7 *vs.* 9). In view of these results, the low yields of **4g** and **4i** can be attributed to the hydrolysis of the intermediates arising from them because of their relatively high water-solubility.

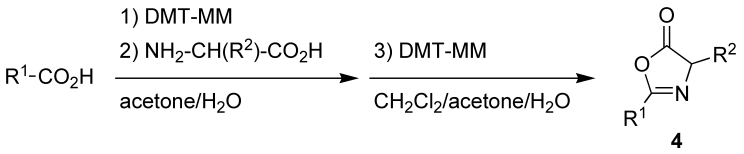
Because oxazol-5(4*H*)-ones bearing a hydrogen at the 4-position readily undergo tautomerization to the corresponding oxazoles,[20,21] 4-monosubstituted oxazolones are generally obtained as a racemic mixture even though they are prepared from optically active amino acids. In most cases, however, such racemic mixtures can be utilized in subsequent reactions.[1–4,21] In our case, **4b** was obtained as a diastereomeric mixture (d.r.=1 : 1, determined by ^{1}H-NMR), which is consistent with the general tendency of oxazolones to racemize, and thus, other oxazolones were probably also produced as racemic mixtures.

Finally, because oxazoles are also an important class of heterocyclic compounds,[22–24] we attempted the preferential synthesis of 2,4-disubstituted-5-(4,6-dimethoxy-1,3,5-triazin-2-yloxy)oxazoles **5** by modifying the present one-pot method. As described above, the conversion of oxazolones **4** to oxazoles **5** could be promoted by the deprotonation of **4** or their enol form with a strong base. Thus, we conducted the second reaction without the addition of DEA·HCl using two or more equivalents of DMT-MM. As shown in Chart 3, oxazole derivatives **5b** and **5c** were successfully obtained in 80% and 57% yields, respectively. Thus, DMT-MM plays three roles in the synthesis of **5**. Although similar reactions giving oxazoles possessing the *tert*-butoxycarbonyloxy,[25] diphenylphosphoryloxy, or *N*,*N*,*N*′,*N*′-tetramethylamidiniooxy[26] group at the 5-position have been reported in the cyclodehydration of *N*-acylamino acids with $(Boc)_2O$, diphenyl chlorophosphate (DPCP), or chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium chloride, respectively, these reactions did not occur in aqueous solvents. The reaction for the synthesis of *O*-Boc-oxazoles could not be stopped at the oxazolones forming stage. In marked contrast, our present synthesis enables the selective formation of either oxazolones or oxazoles.

Conclusion

In conclusion, we have succeeded in developing a one-pot method for the synthesis of oxazolones or oxazoles from amino acids using DMT-MM. This method is applicable to various kinds of amino acids and provides convenient access

Table 2. One-Pot Synthesis of the Oxazolones **4** Using DMT-MM in Aqueous Solvents



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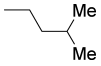
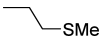
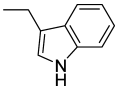
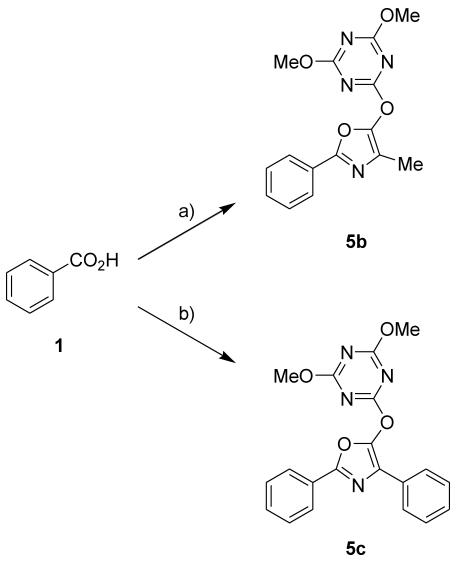
Entry	Product number	R^1	Amino acid	R^2	Reaction time (h)		Yield (%)[c]	
					Time 1[a]	Time 2[b]	Oxazolone	Oxazole derivative
1	**4a**	Ph	L-Leucine		4.5	5	71	2
2	**4b**	Ph	L-Isoleucine		10	4	79[d]	nd
3	**4c**	Ph	L-Valine		7.5	4	76	nd
4	**4d**	Ph	L-Phenylalanine		8	6	75	3
5	**4e**	Ph	L-Methionine		6.5	4.5	73	nd
6	**4f**	Ph	L-Tryptophan		3	8	71	4
7	**4g**	Ph	L-Alanine	–Me	12.5	8	37	2
8	**4g**[e]	Ph	L-Alanine	–Me	30	2	54	3
9	**4h**	1-Naphthyl	L-Alanine	–Me	109	6	53	1
10	**4i**	Ph	Glycine	–H	25	6	35	2
11	**4i**[e]	Ph	Glycine	–H	9	2.5	41	5

a) The reaction time for the first reaction (*N*-acylation). *b*) The reaction time for the second reaction (cyclodehydration). *c*) Yields were determined by ^{1}H-NMR. All the crude reaction mixtures found to contain an activated triazinyl ester of starting carboxylic acids in a range of 4% (Entry 10) to 11% (Entry 1). *d*) A mixture of the diastereomeric isomers (d.r.=1 : 1). *e*) An excess (2.5 eq) of DMT-MM was used for the cyclodehydration.



a) i) DMT-MM (1.05 eq), *N*-methylmorpholine (0.20 eq), acetone/H_2O (3 : 1), rt, 15 min; ii) L-alanine (1.1 eq), NaOH (1.1 eq), acetone/H_2O (1 : 1), rt, 13 h; iii) DMT-MM (3.5 eq), *N*-methylmorpholine (2.0 eq), CH_2Cl_2/acetone/H_2O (1 : 1 : 1), rt, 6 h, 80%. b) i) DMT-MM (1.05 eq), *N*-methylmorpholine (0.20 eq), acetone/H_2O (3 : 1), rt, 15 min; ii) DL-2-phenylglycine (1.1 eq), NaOH (1.1 eq), acetone/H_2O (1 : 1), rt, 60 h; iii) DMT-MM (2.1 eq), CH_2Cl_2/acetone/H_2O (1 : 1 : 1), rt, 2 h, 57%.

Chart 3. One-Pot Synthesis of Oxazole Derivatives

to synthetically useful oxazolones.

Experimental

General Methods ^{1}H-NMR spectra were recorded on a JEOL JNM-ECS400 and a JNM-ECS600 spectrometer. ^{13}C-NMR spectra were recorded on a JEOL JNM-ECS400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a HORIBA FT-720 FREEXACT-II spectrometer. Mass spectra were measured on a JEOL JMS-SX102A (electron ionization (EI)-MS and FAB-MS) spectrometer. Elemental analyses were carried out with a Yanaco CHN Corder MT-5 instrument.

DMT-MM was prepared from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine according to the literature procedure.[6] *N*,*N*-Diethylaniline hydrochloride was prepared from *N*,*N*-diethylaniline and concentrated HCl. Other chemicals were obtained from commercial sources and used as received unless otherwise noted.

General Procedure for Preparation of Oxazolones DMT-MM (0.525 mmol) was added to a solution of carboxylic acid (0.500 mmol) and *N*-methylmorpholine (0.10 mmol) in acetone/H_2O (1.67 mL : 0.56 mL) at room temperature. After stirring 15–30 min, a solution of amino acid (0.550 mmol) and sodium hydroxide (0.55 mmol) in water (1.11 mL) was added, and the mixture was stirred at room temperature. After the reaction was completed (monitored by TLC), dichloromethane (1.67 mL), *N*,*N*-diethylaniline hydrochloride (0.650 mmol) and DMT-MM (0.550 mmol) were added in order, and the mixture was stirred for 2–8 h at room temperature. The reaction mixture was poured into an organic solvent (hexane, EtOAc, or hexane/EtOAc) (30 mL), successively washed with water twice (30, 10 mL), aqueous 1 M HCl twice (30, 10 mL), water (10 mL), saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to give oxazolone **4a**–**i**.

The oxazolones were purified by column chromatography for analysis, with some losses.

IR, MS, and ^{1}H-NMR spectra of all oxazolones were consistent with the literature.

4-Isobutyl-2-phenyloxazol-5(4*H*)-one (**4a**)[5,6,20,27]: Colorless crystals. mp 55–57°C. ^{1}H-NMR ($CDCl_3$) δ: 8.02–7.98 (2H, m), 7.61–7.46 (3H, m), 4.42 (1H, dd, J=5.5, 9.0 Hz), 2.07 (1H, m), 1.89–1.80 (1H, m), 1.73–1.64 (1H, m), 1.04 (3H, d, J=6.5 Hz), 1.01 (3H, d, J=6.5 Hz). IR ($CHCl_3$) cm^{-1}: 1824, 1655. High resolution (HR)-MS (EI) *m*/*z*: 217.1111 [Calcd for $C_{13}H_{15}NO_2$: 217.1097 (M^+)].

4-[(1*S*)-1-Methylpropyl]-2-phenyl-oxazol-5(4*H*)-one (**4b**)[5]: Colorless oil (a mixture of diastereomers, whose ratio was found to be changed from 1 : 1 to 9 : 10 [=(*SS*) : (*RS*)], after purification by silica-gel column chromatography). ^{1}H-NMR ($CDCl_3$) for the *SS* isomer: δ: 8.03–7.99 (2H, m), 7.60–7.55 (1H, m), 7.52–7.46 (2H, m), 4.37 (1H, d, J=4.7 Hz), 2.20–2.09 (1H, m), 1.62–1.52 (1H, m), 1.44–1.34 (1H, m), 1.07 (3H, d, J=6.9 Hz), 0.97 (3H, t, J=7.4 Hz). ^{1}H-NMR ($CDCl_3$) for the *RS* isomer δ: 8.03–7.99 (2H, m), 7.60–7.55 (1H, m), 7.52–7.46 (2H, m), 4.42 (1H, d, J=4.0 Hz), 2.20–2.09 (1H, m), 1.75–1.64 (1H, m), 1.52–1.40 (1H, m), 1.02 (3H, t, J=7.3 Hz), 0.91 (3H, d, J=6.9 Hz). IR ($CHCl_3$) cm^{-1}: 1820, 1653. HR-MS (EI) *m*/*z*: 217.1107 [Calcd for $C_{13}H_{15}NO_2$: 217.1103 (M^+)].

4-Isopropyl-2-phenyloxazol-5(4*H*)-one (**4c**)[5,6,20,27]: Colorless crystals. mp 49–52°C. ^{1}H-NMR ($CDCl_3$) δ: 8.04–8.00 (2H, m), 7.61–7.55 (1H, m), 7.52–7.47 (2H, m), 4.30 (1H, d, J=4.7 Hz), 2.46–2.33 (1H, m), 1.15 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=7.0 Hz). IR ($CHCl_3$) cm^{-1}: 1820, 1655. HR-MS (EI) *m*/*z*: 203.0943 [Calcd for $C_{12}H_{13}NO_2$: 203.094 (M^+)].

4-Benzyl-2-phenyloxazol-5(4*H*)-one (**4d**)[5,6,14,20,27]: White solid. mp 72–74°C. ^{1}H-NMR ($CDCl_3$) δ: 7.94–7.90 (2H, m), 7.57–7.52 (1H, m), 7.48–7.42 (2H, m), 7.29–7.17 (5H, m), 4.69 (1H, dd, J=5.0, 7.0 Hz), 3.37 (1H, dd, J=5.0, 14.0 Hz), 3.19 (1H, dd, J=7.0, 14.0 Hz). IR ($CHCl_3$) cm^{-1}: 1821, 1657. HR-MS (EI) *m*/*z*: 251.0949 [Calcd for $C_{16}H_{13}NO_2$: 251.0941 (M^+)].

4-[2-(Methylsulfanyl)ethyl]-2-phenyloxazol-5(4*H*)-one (**4e**)[5,20]: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.02–7.98 (2H, m), 7.61–7.56 (1H, m), 7.52–7.46 (2H, m), 4.61 (1H, dd, J=6.0, 7.5 Hz), 2.74 (2H, t, J=7.1 Hz), 2.37–2.27 (1H, m), 2.20–2.09 (1H, m), 2.12 (3H, s). IR ($CHCl_3$) cm^{-1}: 1828, 1653. HR-MS (EI) *m*/*z*: 235.0661 [Calcd for $C_{12}H_{13}NO_2$: 235.0662 (M^+)].

4-[(1*H*-Indol-3-yl)methyl]-2-phenyloxazol-5(4*H*)-one (**4f**)[5]: Colorless crystals. mp 148–149°C. ^{1}H-NMR ($CDCl_3$) δ: 8.01 (1H, brs), 7.91–7.86 (2H, m), 7.74–7.70 (1H, m), 7.55–7.49 (1H, m), 7.45–7.39 (2H, m), 7.32–7.28 (1H, m), 7.18–7.09 (3H, m), 4.76 (1H, dd, J=5.0, 6.1 Hz), 3.53 (1H, dd, J=5.0, 14.8 Hz), 3.41 (1H, dd, J=6.1, 14.8 Hz). IR ($CHCl_3$) cm^{-1}: 1817, 1655. HR-MS (EI) *m*/*z*: 290.1057 [Calcd for $C_{18}H_{14}N_2O_2$: 290.1050 (M^+)].

4-Methyl-2-phenyloxazol-5(4*H*)-one (**4g**)[5,6,14,20,27]: White solid. mp 44°C. ^{1}H-NMR ($CDCl_3$) δ: 8.03–7.98 (2H, m), 7.61–7.56 (1H, m), 7.53–7.47 (2H, m), 4.46 (1H, q, J=7.6 Hz), 1.60 (3H, d, J=7.6 Hz). IR ($CHCl_3$) cm^{-1}: 1817, 1655. HR-MS (EI) *m*/*z*: 175.0635 [Calcd for $C_{10}H_9NO_2$: 175.0628 (M^+)].

4-Methyl-2-(naphthalen-1-yl)oxazol-5(4*H*)-one (**4h**)[5]: White solid. mp 87–88°C. ^{1}H-NMR ($CDCl_3$) δ: 9.26 (1H, d, J=8.8 Hz), 8.17 (1H, dd, J=1.2, 8.1 Hz), 8.05 (1H, d, J=8.1 Hz), 7.92 (1H, d, J=8.0 Hz), 7.69–7.64 (1H, m), 7.61–7.54 (2H, m), 4.62 (1H, q, J=7.5 Hz), 1.69 (3H, d, J=7.9 Hz). IR ($CHCl_3$) cm^{-1}: 1817, 1647. HR-MS (EI) *m*/*z*: 225.0789 [Calcd for

$C_{14}H_{11}NO_2$: 225.0790 (M^+)].

2-Phenyloxazol-5(4*H*)-one (**4i**)[14,27]: Colorless crystals. mp 89–90°C. ^{1}H-NMR ($CDCl_3$) δ: 8.02–7.98 (2H, m), 7.62–7.56 (1H, m), 7.53–7.47 (2H, m), 4.43 (2H, s). IR ($CHCl_3$) cm^{-1}: 1826, 1655. HR-MS (EI) *m/z*: 161.0479 [Calcd for $C_9H_7NO_2$: 161.0477 (M^+)].

Synthesis of *N*-Benzoyl-leucine (3a)[5] DMT-MM (145.2 mg, 0.525 mmol) was added to a solution of benzoic acid **1a** (61.1 mg, 0.500 mmol) and *N*-methylmorpholine (10.1 mg, 0.10 mmol) in acetone/H_2O (1.67 mL : 0.56 mL) at room temperature. After stirring 15 min, a solution of L-leucine (72.3 mg, 0.551 mmol) and sodium hydroxide (0.55 mmol) in water (1.11 mL) was added, and the mixture was stirred for 12 h at room temperature. EtOAc (30 mL) was added to the reaction mixture and extracted with saturated aqueous $NaHCO_3$ four times. The combined aqueous phase was acidified with 6 M aqueous HCl to pH 1–2, and extracted with $CHCl_3$ (10 mL) six times. The combined organic layer was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The resultant solid was recrystallized from hexane–$CHCl_3$ to give **3a** (107.4 mg, 91%) as colorless crystals. ^{1}H-NMR (DMSO-d_6) δ: 12.57 (1H, br s), 8.60 (1H, d, J=8.0 Hz), 7.91–7.86 (2H, m), 7.58–7.52 (1H, m), 7.51–7.44 (2H, m), 4.48–4.40 (1H, m), 1.83–1.62 (2H, m), 1.62–1.54 (1H, m), 0.92 (3H, d, J=6.5 Hz), 0.87 (3H, d, J=6.5 Hz). IR ($CHCl_3$) cm^{-1}: 3440, 1726, 1660, 1518. HR-MS (FAB) *m/z*: 236.1298 {Calcd for $C_{13}H_{18}NO_3^+$: 236.1281 [$(M+H)^+$]}. Consistent with data reported in the literature. The optical purity of the product was not confirmed.

Synthesis of 2-(4-Methyl-2-phenyloxazol-5-yloxy)-4,6-dimethoxy-1,3,5-triazine (5b) DMT-MM (145.2 mg, 0.525 mmol) was added to a solution of benzoic acid **1a** (61.1 mg, 0.500 mmol) and *N*-methylmorpholine (10.1 mg, 0.10 mmol) in acetone–H_2O (1.67 mL : 0.56 mL) at room temperature. After stirring 15 min, a solution of L-alanine (49.0 mg, 0.550 mmol) and sodium hydroxide (0.55 mmol) in water (1.11 mL) was added, and the mixture was stirred for 13 h at room temperature. Dichloromethane (1.67 mL), *N*-methylmorpholine (110 μL, 1.00 mmol) and DMT-MM (484.2 mg, 1.75 mmol) were added in order, and the mixture was stirred for 6 h at room temperature. The reaction mixture was poured into EtOAc (30 mL), successively washed with water twice (30, 10 mL), aqueous 1 M HCl (30 mL), water (10 mL), saturated aqueous $NaHCO_3$ (30 mL), water (10 mL), saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc=4 : 1) to give oxazole derivative **5b** (125.8 mg, 80%) as a white solid. mp 101–103°C. ^{1}H-NMR ($CDCl_3$) δ: 7.98–7.92 (2H, m), 7.47–7.40 (3H, m), 4.03 (6H, s), 2.15 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 174.0, 172.5, 154.8, 146.3, 130.1, 128.7, 127.2, 125.7, 120.5, 55.8, 10.3. IR ($CHCl_3$) cm^{-1}: 1599, 1558. HR-MS (FAB) *m/z*: 315.1094 {Calcd for $C_{15}H_{15}N_4O_4^+$: 315.1088 [$(M+H)^+$]}. *Anal.* Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.28 ; H, 4.56; N, 17.68.

Synthesis of 2-(2,4-Diphenyloxazol-5-yloxy)-4,6-dimethoxy-1,3,5-triazine (5c) DMT-MM (145.3 mg, 0.525 mmol) was added to a solution of benzoic acid **1a** (61.1 mg, 0.500 mmol) and *N*-methylmorpholine (10.1 mg, 0.10 mmol) in acetone/H_2O (1.67 mL : 0.56 mL) at room temperature. After stirring 15 min, a solution of DL-2-phenylglycine (83.1 mg, 0.550 mmol) and sodium hydroxide (0.55 mmol) in water (1.11 mL) was added, and the mixture was stirred for 60 h at room temperature. Dichloromethane (1.67 mL) and DMT-MM (290.6 mg, 1.05 mmol) were added in order, and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into hexane–EtOAc (15 mL : 15 mL), successively washed with water twice (30, 10 mL), aqueous 1 M HCl (30 mL), water (10 mL), saturated aqueous $NaHCO_3$ (30 mL), water (10 mL), saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc= 9 : 1) to give oxazole derivative **5c** (106.6 mg, 57%) as colorless crystals. mp 125°C. ^{1}H-NMR ($CDCl_3$) δ: 8.09–8.02 (2H, m), 7.85–7.81 (2H, m), 7.50–7.45 (3H, m), 7.43–7.37 (2H, m), 7.32–7.27 (1H, m), 4.00 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 174.0, 172.4, 155.1, 145.7, 130.4, 129.9, 128.7, 128.6, 127.8, 127.1, 126.1, 125.8, 123.8, 55.9. IR ($CHCl_3$) cm^{-1}: 1601, 1556. HR-MS (FAB) *m/z*: 377.1254 {(Calcd for $C_{20}H_{17}N_4O_4^+$: 377.1244 [$(M+H)^+$]}. *Anal.* Calcd for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.72; H, 4.30; N, 14.85.

2-(4-Isobutyl-2-phenyloxazol-5-yloxy)-4,6-dimethoxy-1,3,5-triazine (5a) Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.98–7.93 (2H, m), 7.46–7.40 (3H, m), 4.02 (6H, s), 2.36 (2H, d, J=7.4 Hz), 2.06 (1H, m), 0.94 (6H, d, J=6.9 Hz). IR ($CHCl_3$) cm^{-1}: 1599, 1558. HR-MS (FAB) *m/z*: 357.1565 {Calcd for $C_{18}H_{21}N_4O_4^+$: 357.1557 [$(M+H)^+$]}.

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References and Notes

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