Reaction of Cyclic Imidates with α,β-Unsaturated Esters: Synthesis of New Pyrrolo[2,1-*b*]-1,3-oxazine and Pyrido[2,1-*b*]-1,3-oxazine Derivatives

Shogo Ihara,* Takashi Soma, Daigo Yano, Shunichi Aikawa, and Yasuhiko Yoshida*

Department of Applied Chemistry, Faculty of Science and Engineering, Toyo University, Kujirai, Kawagoe, Saitama 350-8585, Japan
*E-mail: iharayh@toyonet.toyo.ac.jp or yoshida_y@toyonet.toyo.ac.jp

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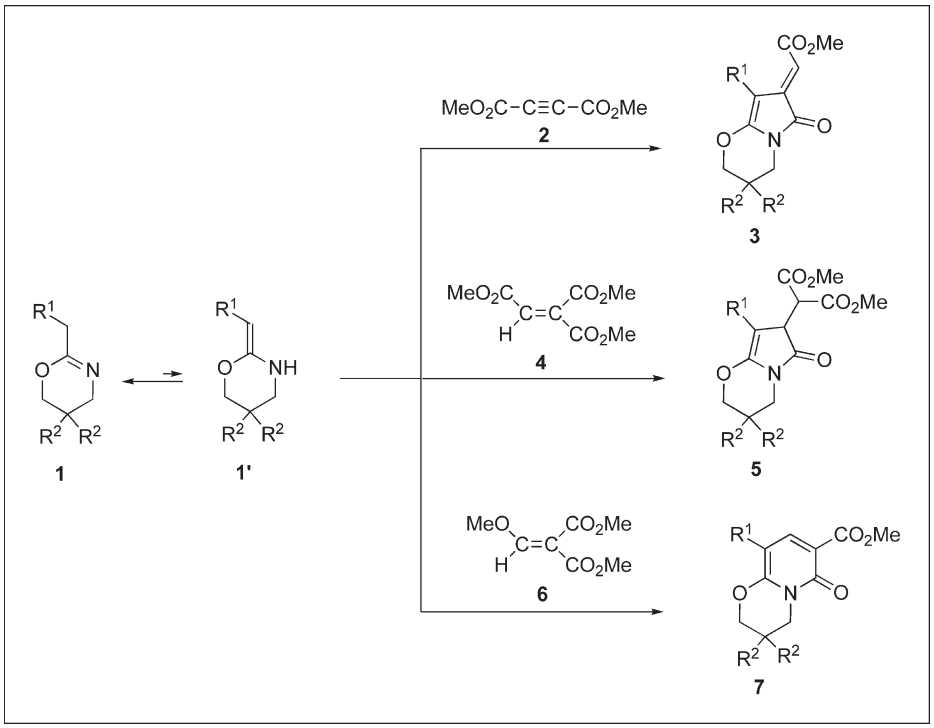

The cycloaddition reaction of cyclic imidates, 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines **1a-f**, with dimethyl acetylenedicarboxylate **2**, trimethyl ethylenetricarboxylate **4**, or dimethyl 2-(methoxymethylene)malonate **6** afforded new fused heterocyclic compounds, such as methyl (6-oxo-3,4-dihydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-ylidene)acetates **3a-f** (71–79%), dimethyl 2-(6-oxo-3,4,6,7-tetrahydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-yl)malonates **5b-f** (43–71%), or methyl 6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*]-1,3-oxazine-7-carboxylates **7a-f** (32–59%), respectively. In these reactions, **1a-f** (cyclic imidates, iminoethers) functioned as their *N,C*-tautomers (enaminoethers) **1′** to α,β-unsaturated esters **2**, **4,** and **6** to give annulation products **3**, **5**, and **7** following to the elimination of methanol, respectively.

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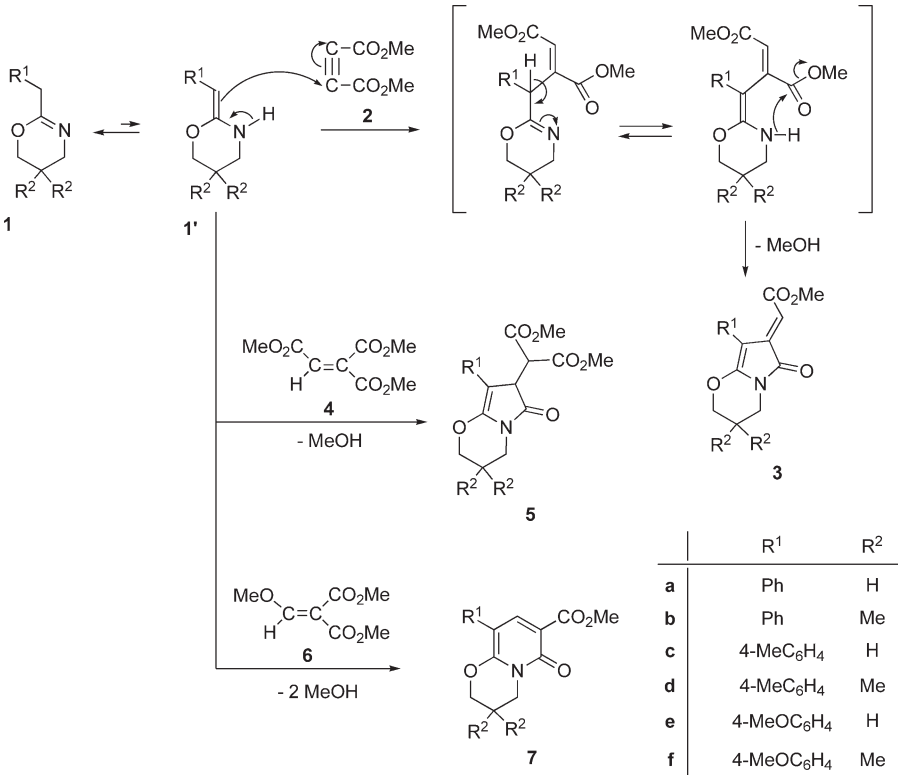
INTRODUCTION

In 1972, Toke *et al*. [1] first described an existence of tautomerism by the chemical terms of iminoether-enaminoether tautomerism for *N,C*-tautomerism of substituted acetimidates in their report. The existence of *N,C*-tautomerism of cyclic imidates was demonstrated by Pfau *et al*. [2] on the basis of ^{1}H NMR technique, in which 2-(benzylimino)-3-methyltetrahydropyran or 2-(benzylimino)-3-methyltetrahydrofuran reacted with α,β-unsaturated esters or 3-buten-2-one to give conjugate addition products combined at α-carbon relative to imino group, respectively. On a *C*-alkylation of enaminoether, Trost *et al*. [3] reported the reaction of 6-methoxy-1-methyl-1,2,3,4-tetrahydropyridine with 3-buten-2-one to afford conjugate addition product. To our best knowledge, however, there is no report to use cyclic imidates as their *N,C*-tautomers, which reacted with α,β-unsaturated esters to form fused heterocycles.

In this study, we expected the synthesis of novel fused heterocycles, which shared a common molecular skeleton, consisting of fused oxazine and pyrrolidine hetercycles. Herein, we report the easy and efficient synthesis of new *N*-bridged fused heterocycles, methyl

Scheme 1



	R^1	R^2
a	Ph	H
b	Ph	Me
c	4-MeC_6H_4	H
d	4-MeC_6H_4	Me
e	4-$MeOC_6H_4$	H
f	4-$MeOC_6H_4$	Me

(6-oxo-3,4-dihydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-ylidene) acetates **3**, dimethyl 2-(6-oxo-3,4,6,7-tetrahydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-yl)malonates **5** and methyl 6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*]-1,3-oxazine-7-carboxylates **7** from the cycloaddition reaction of the cyclic imidates, 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines **1** with dimethyl acetylenedicarboxylate **2**, trimethyl ethylenetricarboxylate **4** or dimethyl 2-(methoxymethylene)malonate **6**, respectively.

RESULTS AND DISCUSSION

The reaction of the cyclic imidates **1a-f** with dimethyl acetylenedicarboxylate **2** at room temperature afforded (6-oxo-3,4-dihydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-ylidene) acetates **3a-f** in good yields (71–79%). As shown in Scheme 1, cyclic imidates (imino ether) **1a-f** isomerized to their enaminoethers **1′** and attacked to dimethyl acetylenedicarboxylate **2** to yield the Michael adducts. The adducts isomerized to enaminoethers again, followed by cyclization with elimination of methanol to yield **3a-f**. The compounds, **3a-f**, were characterized by ^{1}H NMR, ^{13}C NMR, MALDI-TOF-MS spectral, and elemental analysis data. *E*-Forms of **3a-f** were identified by the characteristic signals for the olefinic hydrogen atoms on the acetate moieties at δ 6.15–6.19 in ^{1}H NMR spectrum [4]. In addition, the compounds, 5a-f, were analyzed by means of HMBC in NMR technique. As shown in Table 1, the reaction of 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines **1** with α,β-unsaturated esters **4** or **6** provided 2-(6-oxo-3,4,6,7-tetrahydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-yl)malonates **5a-f** in good yields (43–71%) or 6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*]-1,3-oxazine-7-carboxylates **7a-f** in moderate yields (32–59%), respectively, by the similar reaction path giving compounds **3**. It was difficult for the compound **5a** to be purified by means of distillation, crystallization or silica gel chromatography. Also, *N*-alkylation-cyclization products were not found in these cycloaddition reactions. It was concluded that their enaminoethers **1′** as *N,C*-tautomer of the iminoether (cyclic imidates) **1** reacted with α,β-unsaturated

Table 1

Yields of compounds **3**, **5**, and **7**.

			Compounds		
	R^1	R^2	**3** (%)	**5** (%)	**7** (%)
a	Ph	H	74	54[a]	38
b	Ph	Me	76	69	55
c	4-MeC_6H_4	H	75	43	40
d	4-MeC_6H_4	Me	79	59	59
e	4-$MeOC_6H_4$	H	71	46	32
f	4-$MeOC_6H_4$	Me	74	71	49

[a] Crude product.

esters **2**, **4**, and **6** to give new *C*-alkylation-cyclization products **3**, **5**, and **7**, respectively.

EXPERIMENTAL

All melting points were provided with uncorrected measurement. IR spectra were recorded on a Horiba FT-720 spectrometer as potassium bromide pellets. ^{1}H and ^{13}C NMR data were obtained using a JEOL JNM-ECX500M (500 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (0.03%) as an internal standard. For compounds **3**, **5**, and **7** MALDI-TOF-MS spectra were recorded on a Bruker AutoFlex II TOF/TOF mass spectrometer equipped with a nitrogen laser (λ = 337 nm), a pulsed ion extraction and a reflector. The operation was performed at an accelerating potential of 20 kV for a reflector positive ion mode. Samples for the MALDI analysis were prepared by mixing volumes of the matrix solution β-methyl-*trans*-cinnamylidenemalononitrile, called as BMCM [5] (10 mg/mL in THF), sample solution (2 mg/mL in $CHCl_3$), and cationization reagent solution (2 mg/mL in THF) to obtain a 20:1:8 ratio (BMCM/sample/TFANa) v/v. Elemental analyses were performed using a Perkin-Elmer 2400 II CHN Analyzer.

Starting materials. 2-Benzyl-5,6-dihydro-4*H*-1,3-oxazines **1a-f** were prepared by modifying the literature procedure [6]. A mixture of arylacetoimidates [7] and corresponding 3-aminopropanols in diglyme was refluxed at 120°C (oil bath), and then distilled under reduced pressure.

2-Benzyl-5,6-dihydro-4H-1,3-oxazine (1a) [8]. The product was collected as colorless oil; 78% yield; bp 100–112°C (1.2 Torr); ^{1}H NMR: δ 1.82 (2H, quin, J = 5.7 Hz, CH_2), 3.37 (2H, t, J = 5.7 Hz, NCH_2), 3.43 (2H, s, Ar—CH_2), 4.10 (2H, t, J = 5.6 Hz, OCH_2), 7.20–7.25 (1H, m, Ar—H), 7.28–7.30 (4H, m, Ar—H).

2-Benzyl-5,5-dimethyl-5,6-dihydro-4H-1,3-oxazine (1b). The product was collected as colorless oil; 78% yield; bp 97°C (0.7 Torr); ^{1}H NMR: δ 0.90 (6H, s, 2 × CH_3), 3.08 (2H, t, J = 1.1 Hz, NCH_2), 3.47 (2H, s, Ar—CH_2), 3.67 (2H, t, J = 1.1 Hz, OCH_2), 7.20–7.24 (1H, m, Ar—H), 7.29–7.30 (4H, m, Ar—H).

2-(4-Methylbenzyl)-5,6-dihydro-4H-1,3-oxazine (1c). The product was collected as colorless oil; 63% yield; bp 106–108°C (0.5 Torr); ^{1}H NMR: δ 1.81 (2H, quin, J = 5.7 Hz, CH_2), 2.31 (3H, s, Ar—CH_3), 3.36 (2H, t, J = 5.8 Hz, NCH_2), 3.39 (2H, s, Ar—CH_2), 4.09 (2H, t, J = 5.5 Hz, OCH_2), 7.11 (2H, d, J = 8.0 Hz, Ar—H), 7.17 (2H, d, J = 8.0 Hz, Ar—H).

2-(4-Methylbenzyl)-5,5-dimethyl-5,6-dihydro-4H-1,3-oxazine (1d). The product was collected as colorless oil; 89% yield; bp 105–115°C (0.7 Torr); ^{1}H NMR: δ 0.90 (6H, s, 2 × CH_3), 2.31 (3H, s, Ar—CH_3), 3.07 (2H, s, NCH_2), 3.43 (2H, s, Ar—CH_2), 3.66 (2H, s, OCH_2), 7.10 (2H, d, J = 8.0 Hz, Ar—H), 7.18 (2H, d, J = 8.0 Hz, Ar—H).

2-(4-Methoxybenzyl)-5,6-dihydro-4H-1,3-oxazine (1e). The product was collected as pale yellow oil; 82% yield; bp 120–124°C (0.3 Torr); ^{1}H NMR: δ 1.83 (2H, quin, J = 5.7 Hz, CH_2), 3.36–3.38 (4H, m, overlap of NCH_2 and Ar—CH_2), 4.12 (2H, t, J = 5.6 Hz, OCH_2), 6.84 (2H, d, J = 8.7 Hz, Ar—H), 7.21 (2H, d, J = 8.7 Hz, Ar—H).

2-(4-Methoxybenzyl)-5,5-dimethyl-5,6-dihydro-4H-1,3-oxazine (1f). The product was collected as pale yellow oil; 74% yield; bp 117–120°C (0.2 Torr); ^{1}H NMR: δ 0.90 (6H, s, 2 × CH_3), 3.07 (2H, t, J = 1.1 Hz, NCH_2), 3.41 (2H, s, Ar—CH_2), 3.67 (2H, t, J = 1.1 Hz, OCH_2), 3.78 (3H, s, OCH_3), 6.84 (2H, d, J = 8.7 Hz, Ar—H), 7.21 (2H, d, J = 8.7 Hz, Ar—H).

General procedure for the synthesis of methyl (6-oxo-3,4-dihydro-2*H*-pyrrolo[2,1-*b*]-1,3-oxazin-7-ylidene)acetates 3. To a stirred solution of 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines **1** (30 mmol) in methanol (15 mL) was added dropwise a solution of dimethyl acetylenedicarboxylate **2** (45 mmol) in methanol (15 mL) over 30 min at room temperature. After the reaction mixture was maintained for 15 min at room temperature the precipitated materials were collected by filtration and washed with methanol.

Methyl (E)-(6-oxo-8-phenyl-3,4-dihydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-ylidene)acetate (3a). The product was obtained as red powder; mp 185–187°C; IR: 1716, 1637 cm^{-1}; ^{1}H NMR: δ 2.22 (1H, t, J = 6.3 Hz, C**H**$_A$H$_B$), 2.24 (1H, t, J = 6.3 Hz, CH$_A$**H**$_B$), 3.77 (3H, s, OCH_3), 4.04 (2H, t, J = 6.3 Hz, OCH_2), 4.54 (1H, d, J = 5.4 Hz, NC**H**$_A$H$_B$), 4.57 (1H, d, J = 5.4 Hz, NCH$_A$**H**$_B$), 6.18 (1H, s, CH), 7.13 (1H, t, J = 7.5 Hz, Ar—H), 7.32 (2H, t, J = 8.3 Hz, Ar—H), 7.84 (2H, d, J = 8.5 Hz, Ar—H); ^{13}C NMR: δ 21.7, 43.2, 52.0, 67.6, 93.5, 99.6, 125.2, 125.8, 128.1, 130.8, 142.6, 165.9, 172.1, 180.3; MALDI-TOF MS: 285.1 (M$^+$); Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.37; H, 5.35; N, 4.88.

Methyl (E)-(3,3-dimethyl-6-oxo-8-phenyl-3,4-dihydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-ylidene)acetate (3b). The product was obtained as red powder; mp 173–174°C; IR: 1716, 1645 cm^{-1}; ^{1}H NMR: δ 1.16 (6H, s, 2 × CH_3), 3.74 (2H, s, OCH_2), 3.78 (3H, s, OCH_3), 4.20 (2H, s, NCH_2), 6.19 (1H, s, CH), 7.14 (1H, t, J = 7.5 Hz, Ar—H), 7.33 (2H, t, J = 7.5 Hz, Ar—H), 7.86 (2H, d, J = 8.3 Hz, Ar—H); ^{13}C NMR: δ 23.0, 29.5, 52.0, 54.9, 76.5, 93.4, 99.5, 125.2, 125.9, 128.2, 130.8, 142.9, 165.9, 171.0, 180.4; MALDI-TOF MS: 313.1 (M$^+$); Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.05; H, 6.24; N, 4.49.

Methyl (E)-[6-oxo-8-(4-methylphenyl)-3,4-dihdro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-ylidene]acetate (3c). The product was obtained as red powder; mp 179–180°C; IR: 1730, 1630 cm^{-1}; ^{1}H NMR: δ 2.22 (1H, t, J = 6.3 Hz, C**H**$_A$H$_B$), 2.23 (1H, t, J = 6.3 Hz, CH$_A$**H**$_B$), 2.32 (3H, s, Ar—H), 3.77 (3H, s, OCH_3), 4.03 (2H, t, J = 6.3 Hz, OCH_2), 4.56 (1H, d, J = 5.4 Hz, NC**H**$_A$H$_B$), 4.57 (1H, d, J = 5.4 Hz, NCH$_A$**H**$_B$), 6.18 (1H, s, CH), 7.13 (2H, d, J = 8.0 Hz, Ar—H), 7.72 (2H, d, J = 8.0 Hz, Ar—H); ^{13}C NMR: δ 21.2, 21.9, 43.3, 52.0, 67.5, 93.7, 99.5, 125.9, 127.7, 128.9, 134.8, 142.8, 166.0, 171.9, 180.4; MALDI-TOF MS: 299.1 (M$^+$); Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.45; H, 5.75; N, 4.76.

Methyl (E)-(3,3-dimethyl-[6-oxo-8-(4-methylphenyl)-3,4-dihydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-ylideneacetate (3d). The product was obtained as red powder; mp 188–190°C; IR: 1720, 1639cm^{-1}; ^{1}H NMR: δ 1.14 (6H, s, 2 × CH_3), 2.32 (3H, s, Ar—CH_3), 3.72 (2H, s, OCH_2), 3.78 (3H, s, OCH_3), 4.17 (2H, s, NCH_2), 6.17 (1H, s, CH), 7.14 (2H, d, J = 7.9 Hz, Ar—H), 7.74 (2H, d, J = 7.9 Hz, Ar—H); ^{13}C NMR: δ 21.2, 23.0, 29.5, 52.0, 54.9, 76.4, 93.4, 99.2, 125.9, 127.7, 128.9, 134.8, 143.0, 165.9, 170.9, 180.5; MALDI-TOF MS: 327.1 (M$^+$); Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.91; H, 6.49; N, 4.41.

Methyl (E)-[8-(4-methoxyphenyl)-6-oxo-3,4-dihydro-2H-pyrrolo [2,1-b]-1,3-oxazin-7-ylidene]acetate (3e). The product was obtained as dark red powder; mp 162–164°C; IR: 1728, 1645 cm^{-1}; ^{1}H NMR: δ 2.19 (1H, t, J = 6.3 Hz, C**H**$_A$H$_B$), 2.21(1H, t,

J = 6.3 Hz, $CH_A\mathbf{H_B}$), 3.76 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.99 (2H, t, J = 6.3 Hz, OCH_2), 4.52 (1H, d, J = 5.2 Hz, $NC\mathbf{H_A}H_B$), 4.53 (1H, d, J = 5.2 Hz, $NCH_A\mathbf{H_B}$), 6.15 (1H, s, CH), 6.87 (2H, d, J = 8.9 Hz, Ar—H), 7.77 (2H, d, J = 8.9 Hz, Ar—H); ^{13}C NMR: δ 21.7, 43.2, 52.0, 55.3, 67.6, 93.4, 99.4, 113.6, 123.3, 127.2, 142.8, 157.2, 165.9, 171.7, 180.4; MALDI-TOF MS: 315.1 (M^+); Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.84; H, 5.47; N, 4.52.

Methyl (E)-[8-(4-methoxyphenyl)-3,3-dimethyl-6-oxo-3,4-dihydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-ylidene]acetate (3f). The product was obtained as dark red powder; mp 157–159°C; IR: 1718, 1637 cm^{-1}; ^{1}H NMR: δ 1.15 (6H, s, 2 × CH_3), 3.72 (2H, s, OCH_2), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.18 (2H, s, NCH_2), 6.17 (1H, s, CH), 6.89 (2H, d, J = 8.0 Hz, Ar—H), 7.78 (2H, d, J = 8.0 Hz, Ar—H); ^{13}C NMR: δ 23.0, 29.6, 52.0, 54.9, 55.3, 76.4, 93.2, 99.2, 113.7, 123.3, 127.2, 143.0, 157.2, 166.0, 170.7, 180.5; MALDI-TOF MS: 343.1 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.68; H, 6.08; N, 4.26.

General procedure for the synthesis of methyl 2-(6-oxo-3,4,6,7-tetrahydro-2*H*-pyrrolo-[2,1-*b*]-1,3-oxazin-7-yl)malonates 5. To a stirred solution of trimethyl ethylenetricarboxylate **4** (20 or 30 mmol) in DMF (15 mL) was added dropwise a solution of 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines **1** (20 or 30 mmol) in DMF (15 mL) over 30 min at room temperature. The reaction mixture was refluxed at 100°C (oil bath) for 4–6 h with stirring. After removal of the solvent and low boiling temperature materials under reduced pressure, the precipitated materials were collected by filtration and then washed with ethyl acetate. Samples for analysis were recrystallized from ethyl acetate.

Dimethyl 2-(6-oxo-8-phenyl-3,4,6,7-tetrahydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-yl)-malonate (5a). The mixture of **1a** (20 mmol) and **4** (20 mmol) were stirred for 4 h. The product was obtained as nondistilled crude oil; ^{1}H NMR: δ 2.02–2.13 (2H, m, CH_2), 3.52 (1H, dt, J = 13.2, 6.6 Hz, $NC\mathbf{H_A}H_B$), 3.65 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.93 (1H, d, J = 2.3 Hz, malonate CH), 4.01 (1H, ddd, J = 11.0, 7.5, 4.9 Hz, $OC\mathbf{H_A}H_B$), 4.08 (1H, d, J = 2.3 Hz, COCH), 4.13 (1H, dt, J = 11.0, 6.0 Hz, $OCH_A\mathbf{H_B}$), 4.21 (1H, dt, J = 13.2, 6.6 Hz, $NCH_A\mathbf{H_B}$), 7.20 (1H, t, J = 7.4 Hz, Ar—H), 7.33 (2H, t, J = 4 7. Hz, Ar—H), 7.40 (2H, d, J = 8.3 Hz, Ar—H).

Dimethyl 2-(3,3-dimethyl-6-oxo-8-phenyl-3,4,6,7-tetrahydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-yl)-malonate (5b). The mixture of **1b** (20 mmol) and **4** (20 mmol) were stirred for 4 h to afford **5b** as white powder; mp 157–159°C; IR: 1730, 1686, 1645 cm^{-1}; ^{1}H NMR: δ 1.08 (3H, s, CH_3), 1.09 (3H, s, CH_3), 3.12 (1H, d, J = 12.6 Hz, $NC\mathbf{H_A}H_B$), 3.65 (3H, s, OCH_3), 3.66 (1H, $OC\mathbf{H_A}H_B$ overlapped with OCH_3), 3.75 (3H, s, OCH_3), 3.76 (1H, $OCH_A\mathbf{H_B}$ overlapped with OCH_3), 3.93 (1H, d, J = 2.1 Hz, malonate CH), 4.01 (1H, d, J = 12.6 Hz, $NCH_A\mathbf{H_B}$), 4.09 (1H, d, J = 2.1 Hz, COCH), 7.20 (1H, t, J = 7.5 Hz, Ar—H), 7.33 (2H, t, J = 8.0 Hz, Ar—H), 7.40 (2H, d, J = 8.3 Hz, Ar—H); ^{13}C NMR: δ 23.3, 23.9, 30.7, 43.8, 49.6, 50.6, 52.7, 53.1, 75.9, 93.2, 126.4, 128.2, 128.5, 136.2, 143.8, 164.8, 168.4, 171.6; MALDI-TOF MS: 373.1 (M^+); Anal. Calcd. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.59; H, 6.28; N, 3.77.

Dimethyl 2-[6-oxo-8-(4-methylphenyl)-3,4,6,7-tetrahydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-yl]malonate (5c). The mixture of **1c** (20 mmol) and **4** (20 mmol) were stirred for 4 h to afford **5c** as white powder; mp 109–111°C; IR: 1736, 1697, 1645 cm^{-1}; ^{1}H NMR: δ 2.02–2.14 (2H, m, CH_2), 2.33 (3H, s, Ar—CH_3), 3.50 (1H, dt, J = 13.2, 6.6 Hz, $NC\mathbf{H_A}H_B$), 3.65 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.91 (1H, d, J = 2.2 Hz, malonate CH), 3.99 (1H, dt, J = 11.0, 5.5 Hz, $OC\mathbf{H_A}H_B$), 4.06 (1H, d, J = 2.2 Hz, COCH), 4.11 (1H, ddd, J = 11.0, 7.5, 5.5 Hz, $OCH_A\mathbf{H_B}$), 4.21 (1H, dt, J = 13.2, 6.6 Hz, $NCH_A\mathbf{H_B}$), 7.14 (2H, d, J = 8.1 Hz, Ar—H), 7.29 (2H, d, J = 8.1 Hz, Ar—H); ^{13}C NMR: δ 21.2, 22.7, 38.2, 43.8, 50.6, 52.7, 53.2, 65.5, 93.4, 128.4, 129.0, 133.2, 136.1, 144.4, 164.7, 168.4, 171.7; MALDI-TOF MS: 359.1 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.54; H, 5.99; N, 3.83.

Dimethyl 2-[3,3-dimethyl-6-oxo-8-(4-methylphenyl)-3,4,6,7-tetrahydro-2H-pyrrolo-[2,1-b]-1,3-oxazin-7-yl]malonate (5d). The mixture of **1d** (30 mmol) and **4** (30 mmol) were stirred for 5 h to afford **5d** as white powder; mp 179–181°C; IR: 1730, 1689, 1649 cm^{-1}; ^{1}H NMR: δ 1.07 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.33 (3H, s, Ar—CH_3), 3.10 (1H, d, J = 12.9 Hz, $NC\mathbf{H_A}H_B$), 3.64 (3H, s, OCH_3), 3.64 (1H, d, J = 10.3 Hz, $OC\mathbf{H_A}H_B$), 3.74 (3H, s, OCH_3), 3.74 (1H, d, J = 10.3 Hz, $OCH_A\mathbf{H_B}$), 3.92 (1H, d, J = 2.2 Hz, malonate CH), 4.00 (1H, d, J = 12.9 Hz, $NCH_A\mathbf{H_B}$), 4.07 (1H, d, J = 2.2 Hz, COCH), 7.14 (2H, d, J = 8.0 Hz, Ar—H), 7.29 (2H, d, J = 8.0 Hz, Ar-H); ^{13}C NMR: δ 21.2, 23.3, 23.9, 30.7, 43.8, 49.6, 50.7, 52.6, 53.1, 75.9, 93.3, 128.4, 129.0, 133.2, 136.1, 143.5, 164.8, 168.5, 171.6; MALDI-TOF MS: 387.1 (M^+); Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.29; H, 6.65; N, 3.57.

Dimethyl [8-(4-methoxyphenyl)-6-oxo-3,4,6,7-tetrahydro-2H-pyrrolo[2,1-b]-1,3-oxazin-7-yl]malonate (5e). The mixture of **1e** (30 mmol) and **4** (30 mmol) were stirred for 4 h to afford **5e** as pale yellow powder; mp 136–139°C; IR: 1732, 1689, 1651 cm^{-1}; ^{1}H NMR: δ 2.02–2.14 (2H, m, CH_2), 3.50 (1H, dt, J = 13.2, 6.6 Hz, $NC\mathbf{H_A}H_B$), 3.65 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.91 (1H, d, J = 2.3 Hz, malonate CH), 4.00 (1H, ddd, J = 11.0, 7.5, 4.9 Hz, $OC\mathbf{H_A}H_B$), 4.04 (1H, d, J = 2.3 Hz, COCH), 4.11 (1H, dt, J = 11.0, 5.5 Hz, $OCH_A\mathbf{H_B}$), 4.21 (1H, dt, J = 13.2, 6.6 Hz, $NCH_A\mathbf{H_B}$), 6.87 (2H, d, J = 9.0 Hz, Ar-H), 7.33 (2H, d, J = 9.0 Hz, Ar—H); ^{13}C NMR: δ 22.7, 38.2, 43.9, 50.6, 52.6, 53.2, 55.3, 65.5, 93.2, 113.7, 128.5, 129.7, 144.0, 158.1, 164.6, 168.4, 171.7; MALDI-TOF MS: 375.1 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_7$: C, 60.50; H, 5.64; N, 3.73. Found: C, 60.50; H, 5.70; N, 3.73.

Dimethyl 2-[8-(4-methoxyphenyl)-3,3-dimethyl-6-oxo-3,4,6,7-tetrahydro-2H-pyrrolo-[2,1-b]-1,3-oxazin-7-yl]malonate (5f). The mixture of **1f** (20 mmol) and **4** (20 mmol) were stirred for 6 h to afford **5f** as pale yellow powder; mp 138–141°C; IR: 1732, 1689, 1651 cm^{-1}; ^{1}H NMR: δ 1.07 (3H, s, CH_3), 1.08 (3H, s, CH_3), 3.09 (1H, d, J = 12.9 Hz, $NC\mathbf{H_A}H_B$), 3.64 (3H, s, OCH_3), 3.64 (1H, d, J = 10.6 Hz, $OC\mathbf{H_A}H_B$), 3.74 (1H, d, J = 10.6 Hz, $OCH_A\mathbf{H_B}$), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.92 (1H, d, J = 2.2 Hz, malonate CH), 4.01 (1H, d, J = 12.9 Hz, $NCH_A\mathbf{H_B}$), 4.05 (1H, d, J = 2.2 Hz, COCH), 6.88 (2H, d, J = 8.9 Hz, Ar—H), 7.33 (2H, d, J = 8.9 Hz, Ar—H); ^{13}C NMR: δ 23.3, 23.9, 30.7, 43.9, 49.6, 50.7, 52.6, 53.1, 55.3, 76.0, 93.1, 113.7, 128.5, 129.7, 143.1, 158.1, 164.8, 168.5, 171.6; MALDI-TOF MS: 403.1 (M^+); Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.68; H, 6.31; N, 3.44.

General procedure for the synthesis of methyl 3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*]-1,3-oxazine-7-carboxylates 7. To a stirred solution of dimethyl 2-(methoxymethylene)malonate **6**

(33–40 mmol) in diglyme (15 mL) was added dropwise a solution of 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines **1** (30 mmol) in diglyme (15 mL) at room temperature. The reaction mixture was stirred at 180°C (oil bath) for 8–20 h. After removal of the solvent and low boiling temperature materials under reduced pressure, the precipitated materials were collected by filtration and then washed with ethyl acetate. Samples for analysis were recrystallized from ethyl acetate.

Methyl 6-oxo-9-phenyl-3,4-dihydro-2H,6H-pyrido[2,1-b]-1,3-oxazine-7-carboxylate (7a). The mixture of **1a** (30 mmol) and **6** (40 mmol) were stirred for 8 h to afford **7a** as pale yellow powder; mp 155–156°C; IR: 1728, 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.30 (2H, quin, J = 6.0 Hz, CH_2), 3.89 (3H, s, OCH_3), 4.13 (2H, t, J = 6.3 Hz, OCH_2), 4.40 (2H, t, J = 5.4 Hz, NCH_2), 7.30 (1H, t, J = 6.6 Hz, Ar-H), 7.38–7.43 (4H, m, Ar—H), 8.09 (1H, s, CH); ^{13}C NMR: δ 21.1, 40.2, 52.0, 66.0, 105.5, 108.2, 127.2, 128.4, 129.1, 134.9, 147.8, 156.1, 158.7, 166.3; MALDI-TOF MS: 285.1 (M^+); Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.56; H, 5.30; N, 4.89.

Methyl 3,3-dimethyl-6-oxo-9-phenyl-3,4-dihydro-2H,6H-pyrido[2,1-b]-1,3-oxazine-7-carboxylate (7b). The mixture of **1b** (30 mmol) and **6** (33 mmol) were stirred for 8 h to afford **7b** as pale yellow powder; mp 177–180°C; IR: 1730, 1687, 1662, cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.15 (6H, s, 2 × CH_3), 3.84 (2H, s, OCH_2), 3.89 (3H, s, OCH_3), 4.00 (2H, s, NCH_2), 7.28 (1H, t, J = 6.9 Hz, Ar—H), 7.37–7.42 (4H, m, Ar—H), 8.36 (1H, s, CH); ^{13}C NMR: δ 23.0, 28.3, 51.4, 52.1, 75.1, 105.1, 108.4, 127.2, 128.4, 129.1, 135.0, 147.8, 155.0, 158.8, 166.3; MALDI-TOF MS: 313.1 (M^+); Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.23; H, 6.31; N, 4.44.

Methyl 6-oxo-9-(4-methylphenyl)-3,4-dihydro-2H,6H-pyrido[2,1-b]-1,3-oxazine-7-carboxylate (7c). The mixture of **1c** (30 mmol) and **6** (33 mmol) were stirred for 6 h to afford **7c** as pale yellow powder; mp 188–190°C; IR: 1724, 1655 cm^{-1}; ^1H NMR: δ 2.29 (2H, quin, J = 6.0 Hz, CH_2), 2.38 (3H, s, Ar—CH_3), 3.89 (3H, s, OCH_3), 4.13 (2H, t, J = 6.0 Hz, OCH_2), 4.39 (2H, t, J = 5.5 Hz, NCH_2), 7.20 (2H, d, J = 8.3 Hz, Ar—H), 7.28 (2H, d, J = 8.3 Hz, Ar—H), 8.32 (1H, s, CH); ^{13}C NMR: δ 21.1, 21.2, 40.2, 52.0, 66.0, 105.5, 108.1, 129.0, 129.1, 131.9, 137.0, 147.8, 156.1, 158.7, 166.4; MALDI-TOF MS: 299.1 (M^+); Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.48; H, 5.74; N, 4.73.

Methyl 3,3-dimethyl-6-oxo-9-(4-methylphenyl)-3,4-dihydro-2H,6H-pyrido[2,1-b]-1,3-oxazine-7-carboxylate (7d). The mixture of **1d** (30 mmol) and **6** (40 mmol) were stirred for 8 h to afford **7d** as pale yellow powder; mp 195–196°C; IR: 1728, 1637 cm^{-1}; ^1H NMR: δ 1.15 (6H, s, 2 × CH_3), 2.38 (3H, s, Ar—CH_3), 3.83 (2H, s, OCH_2), 3.89 (3H, s, OCH_3), 3.99 (2H, s, NCH_2), 7.21 (2H, d, J = 8.3 Hz, Ar—H), 7.29 (2H, d, J = 8.3 Hz, Ar—H), 8.34 (1H, s, CH); ^{13}C NMR: δ 21.2, 23.0, 28.3, 51.4, 52.0, 75.0, 105.1, 108.3, 129.0, 129.2, 132.0, 137.0, 147.7, 155.0, 158.8, 166.4; MALDI-TOF MS: 327.1 (M^+); Anal. Calcd. for, $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.98; H, 6.56; N, 4.38.

Methyl 9-(4-methoxyphenyl)-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b]-1,3-oxazine-7-carboxylate (7e). The mixture of **1e** (30 mmol) and **6** (40 mmol) were stirred for 8 h to afford **7e** as pale pink powder; mp 180–182°C; IR: 1724, 1655 cm^{-1}; ^1H NMR: δ 2.29 (2H, quin, J = 6.0 Hz, CH_2), 3.83 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.13 (2H, t, J = 6.0 Hz, OCH_2), 4.39 (2H, t, J = 5.6 Hz, NCH_2), 6.93 (2H, d, J = 8.9 Hz, Ar—H), 7.32 (2H, d, J = 8.9 Hz, Ar—H), 8.30 (1H, s, CH); ^{13}C NMR: δ 21.2, 40.2, 52.0, 55.4, 66.0, 105.3, 108.0, 113.9, 127.2, 130.3, 147.7, 156.0, 158.7, 158.8, 166.4; MALDI-TOF MS: 315.1 (M^+); Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.80; H, 5.46; N, 4.53.

Methyl 9-(4-methoxyphenyl)-3,3-dimethyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b]-1,3-oxazine-7-carboxylate (7f). The mixture of **1f** (30 mmol) and **6** (40 mmol) were stirred for 8 h to afford **7f** as pale pink powder; mp 169–172°C; IR: 1730, 1693, 1664 cm^{-1}; ^1H NMR: δ 1.15 (6H, s, 2 × CH_3), 3.83 (2H, s, OCH_2), 3.84 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.99 (2H, s, NCH_2), 6.93 (2H, d, J = 8.9 Hz, Ar—H), 7.32 (2H, d, J = 8.9 Hz, Ar—H), 8.32 (1H, s, CH); ^{13}C NMR: δ 23.0, 28.3, 51.4, 52.0, 55.4, 75.1, 104.9, 108.3, 113.9, 127.2, 130.2, 147.7, 154.9, 158.7, 158.8, 166.4; MALDI-TOF MS: 343.1 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.71; H, 6.06; N, 4.02.

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