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SYNTHESIS OF MULTI-SUBSTITUTED 1,4-BENZOXAZINE USING AN UMPOLUNG REACTION WITH 2-OXO-1,4-BENZOXAZINE-3-CARBOXYLATES

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Abstract – This report describes a one-pot synthesis of multi-substituted 1,4-benzoxazine derivatives by atom economical *N*,*C*-dialkylation reaction of 1,4-benzoxazine derivatives with various organozinc reagents and ketene silyl acetals (KSA).

INTRODUCTION

1,4-Benzoxazines are known as compounds used for many pharmaceuticals and agrochemicals such as potential anorectic active compound **A** as 5-HT_{2c} receptor agonist,[1] anti-inflammatory agent **B**,[2] anticholesteremic agent **C**,[3] and antibacterial agent **D**[4] (Figure 1). Several syntheses of 1,4-benzoxazine have been reported so far. For example, a three-component Petasis reaction,[5] hetero-Diels-Alder reaction of aldehydes and *o*-benzoquinone imides followed by PCC oxidation,[6] and [4+2] cycloaddition of *o*-benzoquinone imides with ketene enolates.[7] However, there exist few one-pot syntheses of 1,4-benzoxazine derivatives that allow to introduce various substituents freely to nitrogen atom, and therefore, new efficient methods are highly desired.

This paper is dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday.

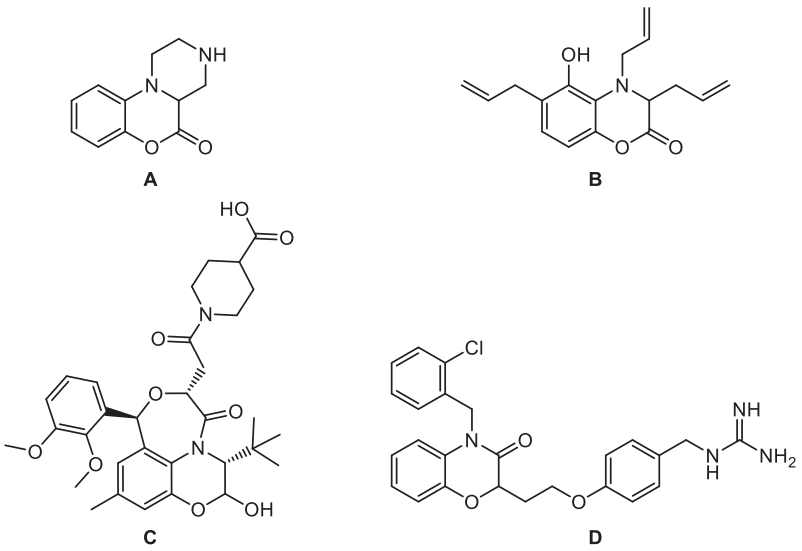
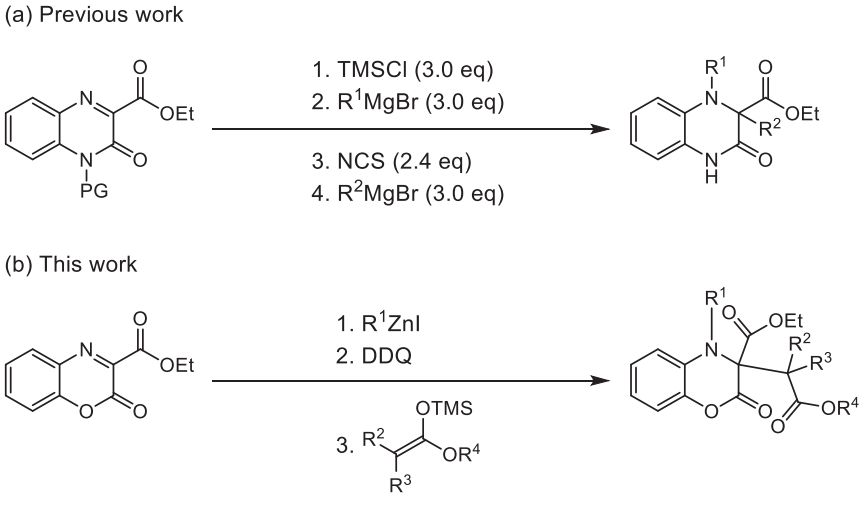


Figure 1. Valuable Compounds Containing a 1,4-Benzoxazine Moiety

An umpolung reaction of an α-imino ester involving nucleophilic addition to the nitrogen atom is difficult due to the electronegativity of the imino group.[8,9] We have developed umpolung reactions of α-imino esters along with various tandem C-C bond-forming reactions using the metal enolate produced as a result of *N*-alkylation.[10] Constructing C-C bonds via subsequent reactions of the resulting enolates remains of interest. Recently, we have reported the tandem *N*-alkylation/oxidation/*C*-alkylation of 3-oxoquinoxaline-2-carboxylate derivatives (Scheme 1(a)), which has some drawbacks; the need of the electron-withdrawing protecting group as the amide and the use of excess Grignard reagents.[11] To extend the utility of this type of reaction, we focused on the new type of α-imino esters, 1,4-benzoxazines. Herein, we report a one-pot synthesis of multi-substituted 1,4-benzoxazine derivatives by atom economical *N*-alkylation/*C*-alkylation reaction with various organozinc reagents and ketene silyl acetals (KSA) (Scheme 1(b)).

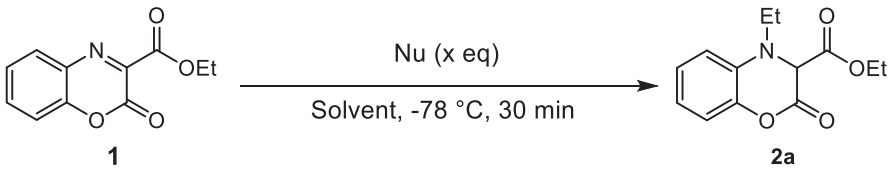


Scheme 1. Previous and the Present Works

RESULTS AND DISCUSSION

Regarding the initial *N*-alkylation step, the optimum reaction conditions were examined using a 1,4-benzoxazine derivative **1**. As shown in Table 1, the reaction of a 1,4-benzoxazine derivative **1** (0.15 mmol) with EtMgBr (1.2 equiv) in EtCN at -78 °C for 30 min led to the formation of *N*-alkylated reaction product **2a** in 12% yield, whereas with Et_2AlCl the reaction gave the desired product in 73% yield (entries 1 and 2). We found that the product **2a** was obtained in 84% yield when EtZnI was used (entry 3). Use of Et_2Zn also showed good reactivity and gave the product **2a** in 88% yield (entry 4). From the examination of the amount of the zinc reagent, use of 1.2 equivs of the organozinc reagent was the most suitable for the present reaction (entries 4–7). Next, various solvents were examined. The use of polar solvents such as THF and DME gave the product in good yields (entries 8 and 9), while using nonpolar solvents such as toluene and CH_2Cl_2 gave the product also in good to high yields (entries 10 and 11).

Table 1. Optimization of the Reaction Conditions



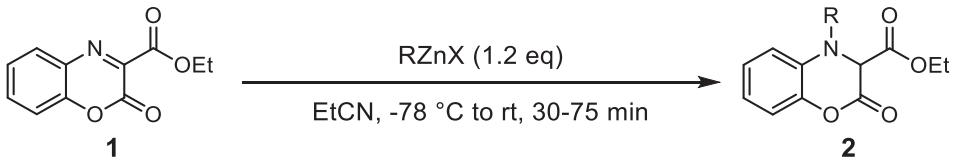
1 **2a**

Entry	Nu (x equiv)	Solvent	Yield (%)
1	EtMgBr (1.2)	EtCN	12
2	Et_2AlCl (1.2)	EtCN	73
3[a]	EtZnI (1.2)	EtCN	84
4	Et_2Zn (1.2)	EtCN	88
5	Et_2Zn (1.0)	EtCN	80
6	Et_2Zn (1.5)	EtCN	82
7	Et_2Zn (2.0)	EtCN	78
8	Et_2Zn (1.2)	THF	77
9	Et_2Zn (1.2)	DME	73
10	Et_2Zn (1.2)	toluene	84
11	Et_2Zn (1.2)	CH_2Cl_2	71

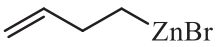
[a] Carried out at -78 °C to rt.

Under the optimized conditions (Table 1, entry 3), use of various organozinc reagents was next examined. Organozinc halides that were easily prepared from alkyl halides were used for the *N*-alkylation reaction instead of dialkylzinc reagents (entries 3–9). A linear *primary*-alkylzinc halide, ^{n}BuZnI and BnZnI gave the desired *N*-alkylation products **2b** and **g** in high yields (entries 3 and 8). *Secondary*-alkyl groups such as ^{i}Pr and ^{c}Hex groups could also be introduced to the imino nitrogen to afford the products **2c** and **d** in high yields (entries 4 and 5). Gratifyingly, even when *tertiary*-alkyl such as a ^{t}Bu derivative was used, the reaction proceeded smoothly to provide the corresponding product **2f** in high yield (entry 7). Moreover, ^{i}Bu, Ph, Me, and homoallyl groups could be introduced and the addition reaction gave the desired products **2e**, **h**, **i**, and **j** in moderate yields (entries 6, 9, 10, 11, and 12). It is noteworthy that this reaction allows to introduce substituents such as Ph and Me groups that were reported to be difficult in the previous *N*-alkylation reactions.[10]

Table 2. Scope of the Organozinc Reagents for the *N*-Alkylation



1 2

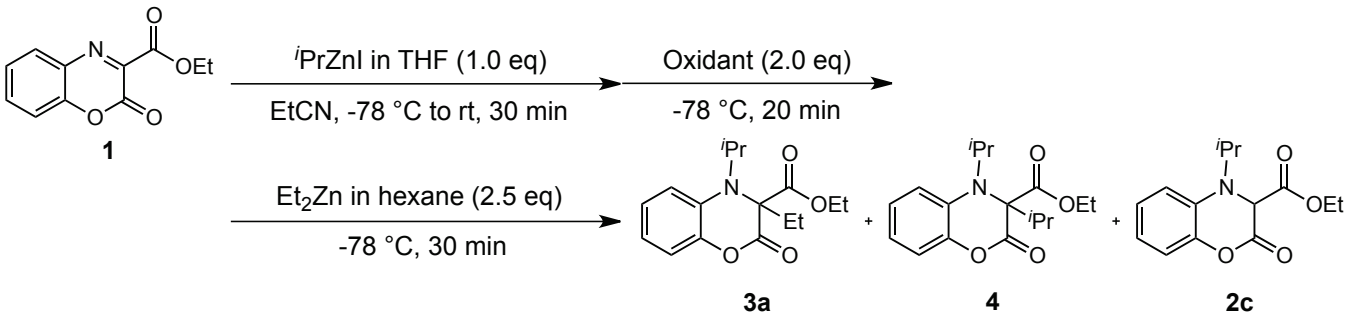
Entry	R_2Zn or RZnX	**2**	Yield (%)	Entry	RZnX	**2**	Yield (%)
1[a]	Et_2Zn	**2a**	93	7	^{t}BuZnI	**2f**	88
2	EtZnI	**2a**	84	8	BnZnI	**2g**	98
3	^{n}BuZnI	**2b**	96	9	PhZnBr	**2h**	66
4	^{i}PrZnI	**2c**	96	10	MeZnBr	**2i**	36
5	^{c}HexZnI	**2d**	91	11	PhZnI・LiCl	**2h**	31
6	^{i}BuZnI	**2e**	64	12		**2j**	56

[a] The reaction was quenched with ^{i}PrOH.

Next, the oxidation of the intermediate enolate into an iminium salt and the subsequent nucleophilic addition of another nucleophile were carried out. Various oxidants were examined first, and the results are summarized in Table 3. When a series of succinimides such as *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS) were used, the desired *N*,*C*-dialkylated product **3a** was obtained in low yields (entries 1–3). When 1,3-dibromo-5,5-dimethylhydatoin (DBDMH) was employed, the reaction provided the product **3a** in 40% yield (entry 4), while use of quinone type oxidants, like 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and chloranil allowed to give the desired products in higher yields than those with the other oxidants (entries 5 and 6). Use of *p*-benzoquinone

which has less oxidizability did not work in the present oxidation step (entry 7). Furthermore, use of other oxidants such as benzoyl peroxide (BPO) and O_2 was also investigated as well, but the desired product was not obtained (entries 8 and 9). As a result of these screening, DDQ was found to be the best oxidant in this tandem reaction.

Table 3. Screening of the Oxidation Reagents

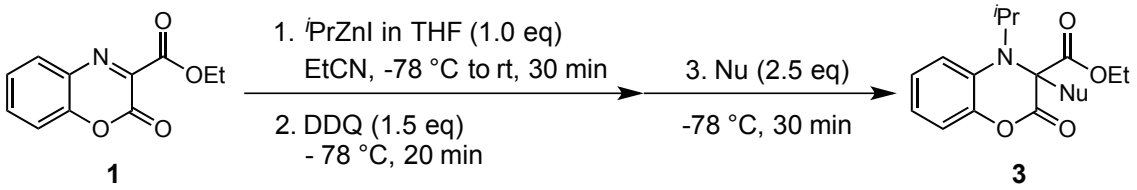


Entry	Oxidant	**3a** (%)	**4** (%)	**2c** (%)
1	NIS	0	0	0
2	NBS	33	6	26
3	NCS	24	10	18
4	DBDMH	40	0	10
5[a]	DDQ	57	4	6
6[a]	chloranil	54	0	0
7[a]	*p*-benzoquinone	0	0	79
8[a]	BPO	0	0	47
9[b]	O_2	0	0	0

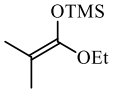
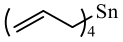
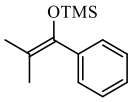
[a] The oxidant (1.5 equiv) was used. [b] O_2 balloon was used.

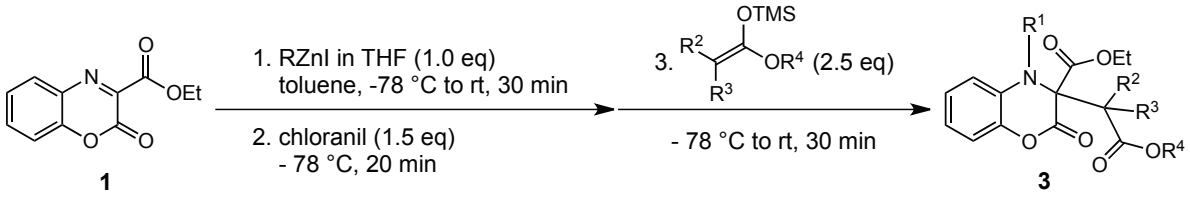
In order to improve the yield of *N*,*C*-dialkylated product, second nucleophiles were investigated and the results are summarized in Table 4. The use of EtZnI showed almost the same reactivity as Et_2Zn (entry 2). Grignard reagent did not work well due to the hydride transfer to the iminium salt to give the reduction by-product (entry 3). Interestingly, dimethylketene ethyl trimethylsilyl acetal was found to be effective in this reaction, giving the desired *N*,*C*-dialkylated product **3b** in 71% yield (entry 4). When tetraallyltin was used, the allylation product **3c** was obtained in moderate yield (entry 5). Silyl enol ether could not give the desired product **3d** presumably due to the low reactivity (entry 6).

Table 4. Optimization of the *N*,*C*-Dialkylation Reaction Conditions

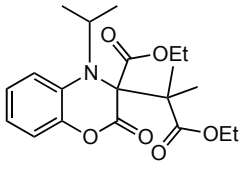


1 **3**

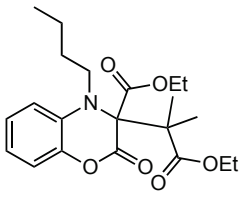
Entry	Nucleophile	**3**	Yield (%)
1	Et_2Zn in hexane	**3a**	57
2	EtZnI in THF	**3a**	55
3	EtMgBr in THF	**3a**	21
4		**3b**	71
5		**3c**	49
6		**3d**	0



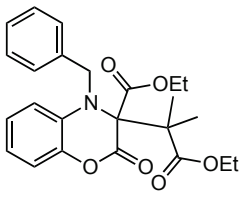
1 **3**



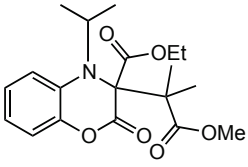
3b 71%[a]



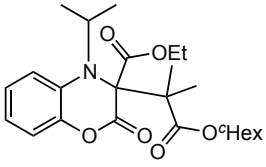
3e 42%[b]



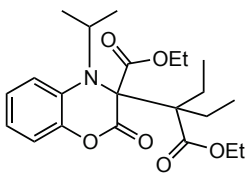
3f 48%[b]



3g 59%



3h 40%

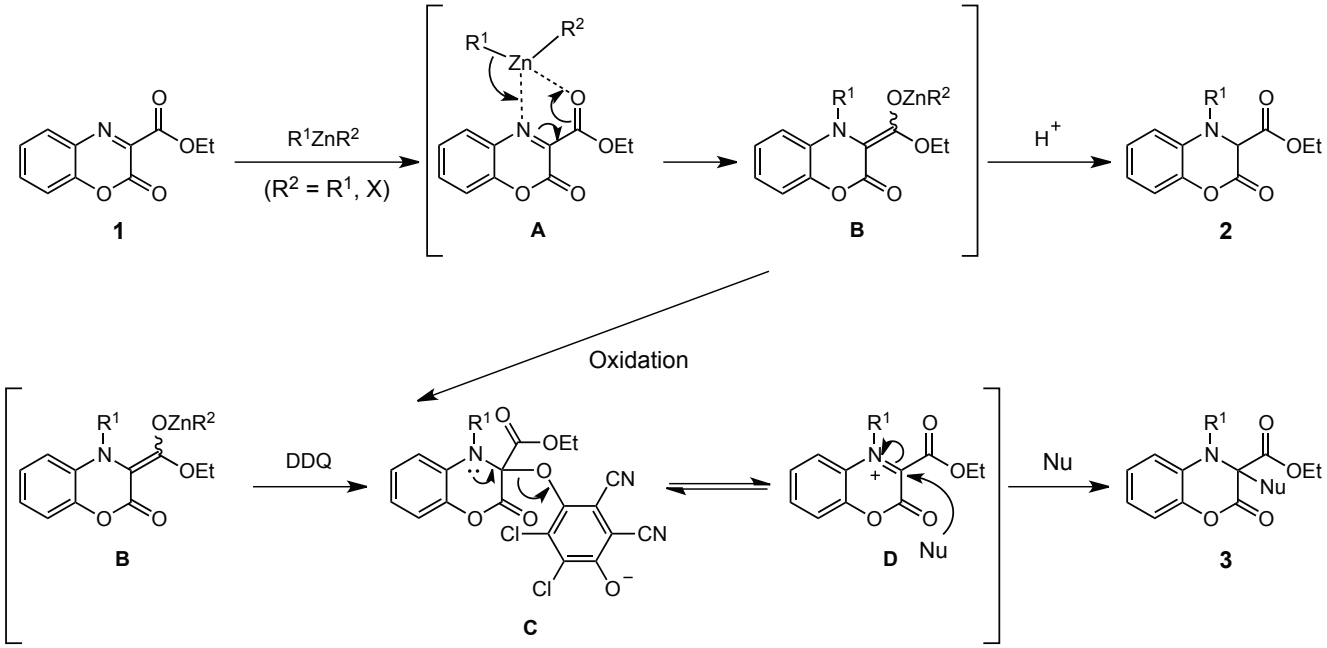


3i 32%

[a] The reaction was carried out under the conditions of Table 4 (entry 4). [b] Chloranil (2.0 equiv) was used.

Scheme 2. Scope of the Second Nucleophiles for *N*,*C*-Dialkylation

The scope of the reaction regarding organozinc reagents or ketene silyl acetals was next examined under the optimized conditions (Scheme 2). The use of chloranil as a oxidant showed good reactivity for the *N*,*C*-dialkylation. Use of *primary*-alkylzinc reagents such as *n*-BuZnI and BnZnI gave the desired products **3e** and **f** in moderate yields. When a series of KSAs were examined, the desired products **3g**, **h**, and **i** were obtained in moderate to good yields.[12,13] A proposed reaction mechanism is shown in Scheme 3.



Scheme 3. Plausible Reaction Mechanism

First, the organozinc reagent coordinates with the imino nitrogen and the carbonyl oxygen atoms to form a five-membered intermediate **A**. *N*-Alkylation of 1,4-benzoxazine derivative **1** generates the zinc enolate **B**. Then hydrolysis of **B** gives *N*-alkylated product **2**. Regarding the *N*,*C*-dialkylation, the zinc enolate **B** is oxidized with DDQ to give the iminium salt **D**. Finally, the iminium salt **D** reacts with the second nucleophile, giving the *N*,*C*-dialkylated product **3**.

CONCLUSIONS

In conclusion, we have developed a one-pot synthesis of multi-substituted 2-oxo-1,4-benzoxazine using an umpolung *N*-alkylation and *N*,*C*-dialkylation. The present method is useful because it could be widely applied to the use of such nucleophiles as secondary/tertiary alkyl zinc reagents, and to the introduction of plural substituents into 1,4-benzoxazine skeletons found in various bioactive compounds in a one-pot procedure.

EXPERIMENTAL

General

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. Propionitrile (EtCN) was distilled from phosphorus pentaoxide and then from calcium hydride and stored over Molecular Sieves 4Å. Tetrahydrofuran (THF) was purified with a Glass Contour Organic Solvent Purification System of Nikko Hansen & Co., Ltd. Dimethoxyethane (DME) was distilled from calcium hydride and then from copper(I) chloride, and stored over sodium. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and stored over Molecular Sieves 4Å. Toluene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4Å. Purification of products was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254). The compounds **1** was prepared according to the reported procedure.[14]

*General procedure: N-Alkylation to α-Imino Ester **1***

Under an argon atmosphere, a suspension of ethyl 2-oxo-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate **1** (32.9 mg, 0.15 mmol) in EtCN (1.0 mL) was stirred at -78 ^{o}C, and to it was added Et_2Zn in *n*-hexane (1.0 M, 0.18 mmol) slowly. After 30 min, the reaction was quenched with sat. $NaHCO_3$ aq (20 mL), and the whole mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (*n*-hexane/EtOAc = 6 / 1) to give the *N*-alkylation product **2**.

Ethyl 4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2a)

Yield 93%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 3.29 (dq, *J* = 13.5, 7.0 Hz, 1H), 3.61 (dq, *J* = 13.5, 7.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.77 (s, 1H), 6.85-6.90 (m, 2H), 7.05-7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.3, 13.9, 43.4, 62.2, 62.3, 113.3, 116.7, 120.0, 125.4, 132.8, 141.3, 161.0, 166.0; IR (neat): 2981, 2938, 1781, 1746, 1613, 1502, 1462, 1271, 1207, 1018, 748, 664, 562 cm^{-1}; HRMS(EI): Calcd for $C_{13}H_{15}NO_4(M)^+$ 249.1001, found 249.1003.

Ethyl 4-butyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2b)

Yield 96%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, *J* = 7.4 Hz, 3H), 1.14 (t, *J* =7.1 Hz, 3H), 1.40 (sext, *J* = 7.4 Hz, 2H), 1.57-1.73 (m, 2H), 3.18 (ddd, *J* = 6.0, 8.3, 14.0 Hz, 1H), 3.57 (ddd, *J* = 5.8, 8.1, 14.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.73 (s, 1H), 6.84-6.88 (m, 2H), 7.12-7.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 13.9, 20.1, 28.9, 48.8, 62.3, 62.9, 113.3, 116.7, 119.9, 125.4, 132.9, 141.3,

160.9, 166.0; IR (neat): 2960, 2934, 2873, 1779, 1747, 1694, 1502, 1462, 1265, 1207, 1018, 747 cm^{-1}; HRMS(EI): Calcd for $C_{15}H_{19}NO_4(M)^+$ 277.1314, found 277.1303.

Ethyl 4-isopropyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2c)

Yield 96%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.14 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.32 (d, *J* = 6.7 Hz, 3H), 4.02 (hept, *J* = 6.7 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.87 (s, 1H), 6.86-6.90 (m, 1H), 6.98-7.01 (m, 1H), 7.03-7.06 (m, 1H), 7.08-7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 20.1, 20.8, 50.3, 58.0, 62.3, 115.7, 116.8, 120.3, 125.2, 132.6, 142.1, 161.3, 166.9; IR (neat): 2979, 2937, 1781, 1750, 1611, 1501, 1462, 1269, 1203, 1113, 1020, 926, 749, 663, 600 cm^{-1}; HRMS(EI): Calcd for $C_{14}H_{17}NO_4(M)^+$ 263.1158, found 263.1162.

Ethyl 4-cyclohexyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2d)

Yield 91%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12-1.21 (m, 4H, including triplet at 1.14 ppm, *J* = 7.1 Hz, 3H), 1.26-1.47 (m, 4H), 1.68-1.71 (m, 1H), 1.81-1.91 (m, 3H), 2.11-2.14 (m, 1H), 3.56 (tt, *J* = 3.3, 11.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.89 (s, 1H), 6.85-6.89 (m, 1H), 6.98-7.00 (m, 1H), 7.03-7.05 (m, 1H), 7.08-7.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 25.5, 25.6, 25.8, 30.9, 31.3, 58.5, 58.7, 62.3, 115.9, 116.8, 120.3, 125.2, 132.7, 142.2, 161.4, 167.0; IR (neat): 2934, 2857, 1779, 1751, 1501, 1457, 1269, 1202, 1047, 1019, 930, 882, 748 cm^{-1}; HRMS(EI): Calcd for $C_{17}H_{21}NO_4(M)^+$ 303.1471, found 303.1474.

Ethyl 4-isobutyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2e)

Yield 64%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.95 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 2.01 (ddhept, *J* = 6.5, 8.4, 6.6 Hz, 1H), 2.84 (dd, *J* = 8.4, 13.9 Hz, 1H), 3.49 (dd, *J* = 6.5, 13.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.69 (s, 1H), 6.84-6.88 (m, 2H), 7.04-7.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 19.9, 20.4, 26.1, 57.1, 62.3, 64.0, 113.4, 116.8, 120.0, 125.4, 133.0, 141.3, 160.8, 166.0; IR (neat): 2963, 2871, 1780, 1741, 1579, 1501, 1466, 1366, 1264, 1202, 1124, 1017, 876, 746 cm^{-1}; HRMS(EI): Calcd for $C_{15}H_{19}NO_4(M)^+$ 277.1314, found 277.1303.

Ethyl 4-(*tert*-butyl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2f)

Yield 88%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 9H), 4.01 (dq, *J* = 7.1, 14.2 Hz, 1H), 4.07 (dq, *J* = 7.1, 14.2 Hz, 1H), 4.92 (s, 1H), 7.05-7.13 (m, 3H), 7.23-7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 28.5, 57.8, 60.4, 62.2, 117.3, 124.1, 125.3, 128.2, 129.7, 147.3, 165.3, 166.5; IR (neat): 2979, 2960, 2853, 1783, 1754, 1487, 1397, 1369, 1260, 1200, 1112, 1032, 757 cm^{-1}; HRMS(EI): Calcd for $C_{15}H_{19}NO_4(M)^+$ 277.1314, found 277.1301.

Ethyl 4-benzyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2g)

Yield 98%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (t, *J* = 7.1 Hz, 3H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.39 (d, *J* = 14.0 Hz, 1H), 4.58 (s, 1H), 4.76 (d, *J* = 14.0 Hz, 1H), 6.89-6.93 (m, 2H), 7.06-7.11 (m, 2H), 7.30-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 52.5, 61.4, 62.3, 113.9, 116.7, 120.6, 125.4, 128.2, 128.4, 129.0, 133.3, 135.0, 141.4, 160.8, 165.8; IR (neat): 2979, 1779, 1751, 1611, 1502, 1462, 1397, 1323, 1269, 1189, 1019, 928, 748 cm^{-1}; HRMS(EI): Calcd for $C_{18}H_{17}NO_4(M)^+$ 311.1158, found 311.1157.

Ethyl 2-oxo-4-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2h)

Yield 66%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, *J* = 7.1 Hz, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.27 (s, 1H), 6.81-7.38 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 62.9, 63.6, 115.3, 117.4, 118.0, 121.1, 122.4, 124.4, 125.2, 129.6, 130.1, 142.4, 143.0, 160.4, 166.1; IR (neat): 2982, 1781, 1748, 1594, 1499, 1374, 1285, 1197, 1105, 1018, 941, 751, 695 cm^{-1}; HRMS(EI): Calcd for $C_{17}H_{15}NO_4(M)^+$ 297.1001, found 297.0996.

Ethyl 4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2i)

Yield 36%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (t, *J* = 7.1 Hz, 3H), 3.05 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.64 (s, 1H), 6.81-6.90 (m, 2H), 7.03-7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 36.4, 62.3, 65.0, 112.9, 116.5, 120.2, 125.5, 133.5, 141.2, 160.5, 165.4; IR (neat): 2983, 1738, 1612, 1504, 1453, 1276, 1200, 1035, 747, 665, 554 cm^{-1}; HRMS(EI): Calcd for $C_{12}H_{13}NO_4(M)^+$ 235.0845, found 235.0849.

Ethyl 4-(but-3-en-1-yl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (2j)

Yield 56%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (t, *J* = 7.1 Hz, 3H), 2.36-2.50 (m, 2H), 3.27 (ddd, *J* = 6.5, 7.5, 13.9 Hz, 1H), 3.67 (ddd, *J* = 6.5, 7.5, 13.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.75 (s, 1H), 5.08-5.16 (m, 2H), 5.80 (tdd, *J* = 6.8, 10.0, 16.8 Hz, 1H), 6.86-6.90 (m, 2H), 7.05-7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 31.2, 48.5, 62.4, 63.0, 113.3, 116.8, 117.4, 120.1, 125.4, 132.6, 134.5, 141.3, 160.7, 166.0; IR (neat): 2981, 2935, 2873, 1779, 1743, 1612, 1502, 1464, 1268, 1207, 1018, 923, 826, 748 cm^{-1}; HRMS(EI): Calcd for $C_{15}H_{17}NO_4(M)^+$ 275.1158, found 275.1168.

*General procedure: Tandem N,C-Dialkylation of α-Imino Ester **1***

Under an argon atmosphere, a suspension of ethyl 2-oxo-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate **1** (32.9 mg, 0.15 mmol) in EtCN (1.0 mL) was stirred at -78 °C, and to it was added *i*-PrZnI in THF (0.95 *N*, 0.15 mmol), which was prepared according to the literature,[15] slowly. The mixture was stirred for 25 min at

-78 °C, and then it was warmed to room temperature and stirred for 5 min. After the mixture was cooled to -78 °C again, DDQ (52.2 mg, 0.23 mmol) in EtCN (1 mL) was added to the reaction mixture. After stirring for 20 min, to it was added nucleophile (2.5 equiv) slowly and the mixture was stirred for 30 min. The reaction was quenched with sat. $NaHCO_3$ aq. (20 mL), and the whole mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (*n*-hexane/EtOAc = 14 / 1) to give the *N*,*C*-dialkylation product **3**.

Ethyl 3-ethyl-4-isopropyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (3a)

Yield 57%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 2.25 (dq, *J* = 7.2, 14.7 Hz, 1H), 2.32 (dq, *J* = 7.2, 14.7 Hz, 1H), 3.57 (hept, *J* = 6.8 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 6.95-7.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.6, 13.7, 18.7, 22.3, 25.5, 48.3, 61.9, 70.7, 116.9, 122.9, 123.0, 124.2, 130.6, 144.9, 166.0, 168.4; IR (neat): 2980, 1751, 1504, 1460, 1298, 1245, 1141, 1100, 1021, 889, 754 cm^{-1}; HRMS(EI): Calcd for $C_{16}H_{21}NO_4(M)^+$ 291.1471, found 291.1459.

Ethyl 3-(1-ethoxy-2-methyl-1-oxopropan-2-yl)-4-isopropyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine-3-carboxylate (3b)

Yield 71%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.49 (s, 3H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.63 (s, 3H), 3.45-3.54 (m, 2H), 3.74-3.84 (m, 1H), 4.17 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.24 (dq, *J* = 7.2, 10.9 Hz, 1H), 6.82-6.87 (m, 1H), 6.94-7.01 (m, 2H), 7.12-7.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.5, 13.6, 20.4, 21.2, 24.2, 25.3, 51.0, 54.1, 61.2, 62.3, 77.5, 116.5, 118.9, 120.5, 124.4, 129.7, 142.7, 163.4, 166.4, 174.4; IR (neat): 2984, 1757, 1614, 1504, 1464, 1387, 1365, 1305, 1248, 1139, 1036, 863, 749 cm^{-1}; HRMS(EI): Calcd for $C_{20}H_{27}NO_6(M)^+$ 377.1838, found 377.1824.

Ethyl 3-allyl-4-isopropyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (3c)

Yield 49%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.39 (d, *J* = 6.7 Hz, 3H), 2.97 (dd, *J* = 7.8, 14.7 Hz, 1H), 3.05-3.10 (m, 1H), 3.66 (hept *J* = 6.7 Hz, 1H), 3.98-4.06 (m, 2H), 5.15-5.17 (m, 1H), 5.22 (dd, *J* = 1.4, 16.9 Hz, 1H), 5.95 (tdd, *J* = 7.8, 10.4, 16.9 Hz, 1H), 6.98-7.08 (m, 3H), 7.14-7.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 18.8, 22.5, 36.9, 48.6, 62.0, 70.5, 117.0, 119.7, 123.3, 124.3, 130.5, 131.4, 145.1, 165.8, 168.1; IR (neat): 3078, 2980, 2937, 1757, 1500, 1461, 1368, 1258, 1223, 1025, 925, 752, 662 cm^{-1}; HRMS(EI): Calcd for $C_{17}H_{21}NO_4(M)^+$ 303.1471, found 303.1459.

Ethyl 4-butyl-3-(1-ethoxy-2-methyl-1-oxopropan-2-yl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (3e)

Yield 42%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, *J* = 7.3 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.71-1.83 (m, 2H), 2.97 (ddt, *J* = 6.9, 11.9, 17.0 Hz, 2H), 3.54-3.73 (m, 4H), 4.24 (dq, *J* = 7.1, 10.6 Hz, 1H), 4.33 (dq, *J* = 7.1, 10.6 Hz, 1H), 6.73-6.79 (m, 2H), 6.95-6.97 (m, 1H), 7.03-7.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 13.6, 13.8, 20.1, 22.2, 24.5, 28.6, 50.3, 51.9, 61.3, 62.6, 114.2, 116.1, 118.9, 125.2, 130.5, 141.1, 162.0, 166.4, 174.4; IR (neat): 2960, 2873, 1758, 1616, 1504, 1391, 1359, 1243, 1148, 1114, 1059, 1030, 863, 746 cm^{-1}; HRMS(EI): Calcd for $C_{21}H_{29}NO_6(M)^+$ 391.1995, found 391.2009.

Ethyl 4-benzyl-3-(1-ethoxy-2-methyl-1-oxopropan-2-yl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine-3-carboxylate (3f)

Yield 48%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 3H), 1.54 (s, 3H), 3.71 (dq, *J* = 7.1, 10.8 Hz, 1H), 3.79 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.04 (dq, *J* = 7.1, 10.7 Hz, 1H), 4.17 (dq, *J* = 7.1, 10.7 Hz, 1H), 4.48 (d, *J* = 17.4 Hz, 1H), 4.91 (d, *J* = 17.4 Hz, 1H), 6.49-6.99 (m, 4H), 7.16-7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3, 13.7, 22.7, 24.9, 51.8, 53.7, 61.4, 62.8, 115.2, 115.8, 119.4, 125.1, 126.7, 127.0, 127.9, 128.3, 130.6, 136.4, 141.0, 161.6, 166.4, 174.7; IR (neat): 2988, 2937, 1758, 1616, 1503, 1456, 1391, 1343, 1243, 1147, 1066, 859, 735, 696 cm^{-1}; HRMS(EI): Calcd for $C_{24}H_{27}NO_6(M)^+$ 425.1838, found 425.1831.

Ethyl 4-isopropyl-3-(1-methoxy-2-methyl-1-oxopropan-2-yl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine-3-carboxylate (3g)

Yield 59%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.48 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.64 (s, 3H), 3.24 (s, 3H), 3.46 (hept, *J* = 6.8 Hz, 1H), 4.18 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.24 (dq, *J* = 7.1, 10.8 Hz, 1H), 6.83-6.87 (m, 1H), 6.97-7.02 (m, 2H), 7.12-7.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.5, 20.4, 21.2, 24.3, 25.2, 51.0, 52.0, 54.3, 62.3, 116.6, 118.9, 120.5, 124.5, 129.5, 142.6, 163.5, 166.3, 174.8; IR (neat): 2986, 2952, 1755, 1503, 1368, 1307, 1230, 1206, 1136, 1038, 863, 748 cm^{-1}; HRMS(EI): Calcd for $C_{19}H_{25}NO_6(M)^+$ 363.1682, found 363.1670.

Ethyl 3-[1-(cyclohexyloxy)-2-methyl-1-oxopropan-2-yl]-4-isopropyl-2-oxo-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazine-3-carboxylate (3h)

Yield 40%; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.18 (t, *J* = 7.2 Hz, 3H), 1.22-1.35 (m, 8H, including doublet at 1.31 ppm, *J* = 7.1 Hz, 3H), 1.47 (s, 3H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.59 (s, 3H), 1.64-1.72 (m, 5H), 3.62 (hept, *J* = 7.1 Hz, 1H), 4.14 (dq, *J* = 7.2, 11.0 Hz, 1H), 4.19 (dq, *J* = 7.2, 11.0 Hz, 1H), 4.45-4.48 (m, 1H), 6.86-6.89 (m, 1H), 6.97-7.01 (m, 2H), 7.13-7.15 (m, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ: 13.5, 20.7, 21.9, 23.4, 23.5, 25.4, 25.6, 30.9, 30.9, 51.1, 53.7, 62.2, 73.6, 116.7, 119.6, 121.0, 124.3, 130.2, 143.4, 163.5, 166.7, 174.1; IR (neat): 2938, 2860, 1757, 1612, 1503, 1459, 1390, 1367, 1306, 1242, 1154, 1037, 864, 745 cm^{-1}; HRMS(EI): Calcd for $C_{24}H_{33}NO_6(M)^+$ 431.2308, found 431.2311.

Ethyl 3-[3-(ethoxycarbonyl)pentan-3-yl]-4-isopropyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (3i)

Yield 32%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, *J* = 7.4 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H), 1.15 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.21-1.29 (m, 6H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.84 (dq, *J* = 7.4, 14.7 Hz, 1H), 2.04 (dq, *J* = 7.4, 14.7 Hz, 1H), 2.19 (dq, *J* = 7.5, 15.8 Hz, 2H), 3.45 (hept, *J* = 6.7 Hz, 1H), 3.63 (dq, *J* = 7.1, 10.5 Hz, 1H), 3.76 (dq, *J* = 7.1, 10.5 Hz, 1H), 4.18 (dq, *J* = 7.1, 10.9 Hz, 1H), 4.26 (dq, *J* = 7.1, 10.9 Hz, 1H), 6.84-6.88 (m, 1H), 6.95-7.03 (m, 2H), 7.18-7.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.1, 10.4, 13.6, 13.9, 20.4, 24.0, 24.6, 26.1, 55.0, 58.9, 60.9, 62.4, 79.4, 116.6, 119.7, 120.9, 124.6, 129.9, 143.2, 163.9, 166.7, 173.1; IR (neat): 2981, 2940, 1758, 1612, 1502, 1499, 1461, 1387, 1367, 1302, 1229, 1132, 1033, 862, 747 cm^{-1}; HRMS(EI): Calcd for $C_{22}H_{31}NO_6(M)^+$ 405.2151, found 405.2138.

Ethyl 3,4-diisopropyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4)

Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.36 (d, *J* = 6.8 Hz, 3H), 2.68 (hept, *J* = 6.8 Hz, 1H), 3.57 (hept, *J* = 6.8 Hz, 1H), 3.95-4.02 (m, 2H), 7.02-7.07 (m, 3H), 7.14-7.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.7, 13.8, 18.7, 22.4, 25.6, 48.3, 61.9, 70.8, 117.0, 123.0, 123.1, 124.2, 130.7, 145.0, 166.1, 168.5; IR (neat): 2980, 2939, 1768, 1747, 1486, 1462, 1370, 1253, 1182, 1025, 890, 755 cm^{-1}; HRMS(EI): Calcd for $C_{17}H_{23}NO_4(M)^+$ 305.1627, found 305.1629.

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12. Although we have not fully understood, one of the reasons for the low yields of the products **3e**, **f**, **h** and **i** may be due to the competing hydrolysis of the intermediary iminium salts.
13. We have not examined the scope of ketene silyl acetals in detail, and results of further examinations will be reported in due course.
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