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Brønsted acid-promoted domino reactions: a novel one-pot three-component synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines

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ABSTRACT

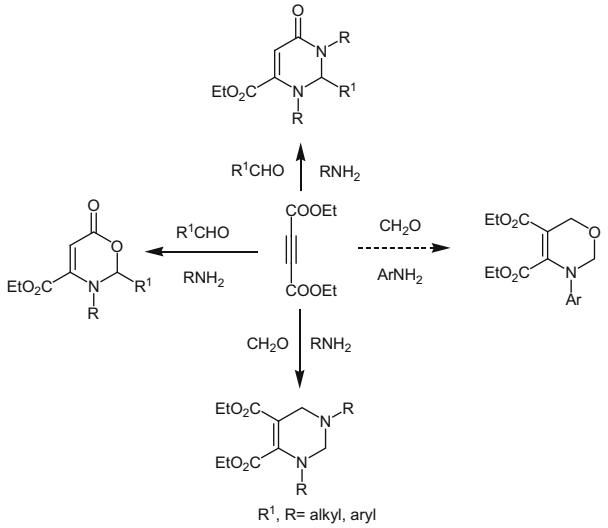
An efficient and novel one-pot synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazine from alkynoates, anilines, and formaldehyde is described. The six-membered *N*,*O*-heterocyclic skeleton was constructed via Brønsted acid-promoted domino hydroamination/Prins reaction/cyclization/dehydration reactions.

The development of simple synthetic routes to widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Consequently, domino reactions including multicomponent reactions (MCRs) have been used as a powerful tool to achieve this goal.[2] At the forefront of these chemical methodologies, these domino processes have created molecular complexity and diversity from readily accessible starting materials in one single operation.[3] The reactants of the one-pot MCRs have been involved in the classical Mannich reaction, which was discovered in 1912[4] and is one of the most important C–C bond-forming reactions for production of nitrogenous molecules.[5] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activity.[6]

Previously, we have reported the preparation of polysubstituted 1,3-oxazine-6-ones[7] and pyrimidines[8] through domino reactions of alkynoates, amine, and aldehydes (Scheme 1). These processes not only represented an elegant procedure for the clean synthesis of polysubstituted *N* or *N*,*O*-heterocycles, but also opened up a new methodology in organic synthesis. The inspiring results prompted us to search for a facile route for the synthesis of other heterocyclic compounds. Various oxazine compounds have been found to show versatile bioactivities,[9] such as antibiotic,[10] antitumor,[11] analgesic,[12] and anticonvulsant activities.[13] Although several methods for the preparation of 1,3-oxazine derivatives have previously been reported,[14,15] few have been focused on the MCRs method.

In this Letter, we would like to report the synthesis of a series of oxazines. According to our retro-synthesis hypothesis (Scheme 2), the 3,6-dihydro-2*H*-1,3-oxazine should be cyclized from intermediate **5** and formaldehyde under certain reaction conditions. In connection with our previous work, intermediate **5** has been successfully formed via the two-component hydroamination and sequential Prins reaction.[14,15] Therefore, the key step in this hypothesis is to screen the suitable reaction conditions for the two-component cyclization and intramolecular dehydration, and we chose Brønsted acids to promote this process.

With this concept in mind, our initial experiment was successful, displaying a modest induction of dimethyl 3-phenyl-3,6-dihydro-2*H*-1,3-oxazine-4,5-dicarboxylate (**4aa**), when we used dichloromethane as a solvent and HCl as the Brønsted acid (Table 1, entry 1). Subsequently, other solvents such as MeOH, MeCN, 1,4-dioxane, toluene, THF, and C_2H_5OH were employed, and the best result was obtained when MeOH was used as solvent with a yield of 74 % (Table 1, entries 2–7). Due to ester exchange reaction, only 38 % of **4aa** was



Scheme 1. Divergent pathways for domino reaction.

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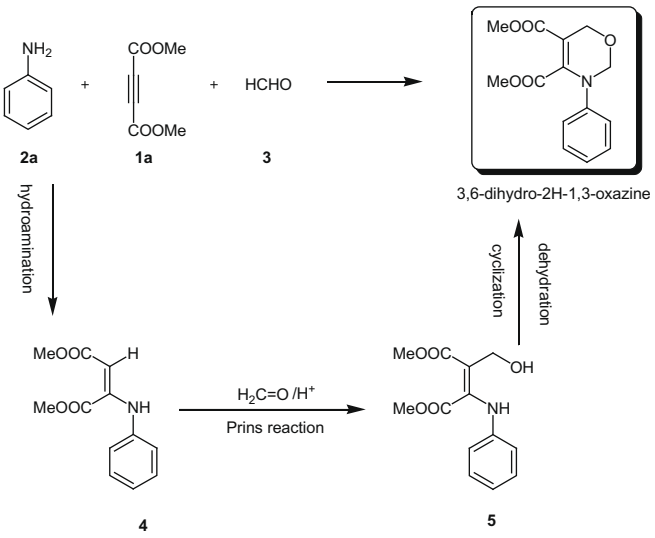
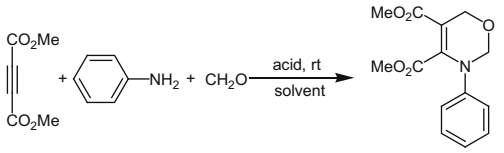


Scheme 2. Proposed mechanism for the domino reaction.

obtained when using C_2H_5OH as solvent (Table 1, entry 7). We also explored the reaction using other acids such as $NaHSO_4$, NaH_2PO_4, and L-proline, and the desired product **4aa** can only be formed in

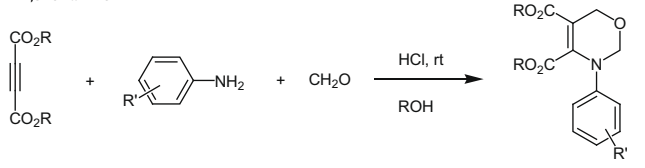
Table 1
Optimization of reaction conditions for the three-component reaction[a]



Entry	Solvent	Acid (mmol)	*t* (h)	Yield[b] (%)
1	CH_2Cl_2	HCl	50	10
2	CH_3OH	HCl	15	74
3	MeCN	HCl	15	24
4	1,4-Dioxane	HCl	15	27
5	Toluene	HCl	15	35
6	THF	HCl	15	32
7	C_2H_5OH	HCl	15	38
8	CH_3OH	$NaHSO_4$	15	53
9	CH_3OH	NaH_2PO_4	15	41
10	CH_3OH	L-Proline	15	58
11	CH_3OH	F_3CCOOH	15	36
12	CH_3OH	HCOOH	15	37

[a] Reaction conditions: dimethyl acetylenedicarboxylate (0.26 mmol), aniline (0.25 mmol), formaldehyde (1.0 mmol), acid (3 mol %).
[b] Determined by GC.

Table 2
Synthesis of 3,4,5-trisubstituted-3,6-dihydro-*2H*-1,3-oxazine[a]



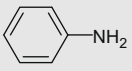
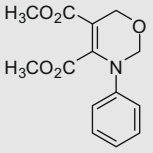
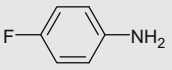
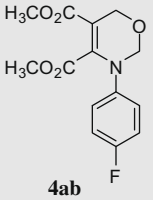
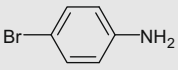
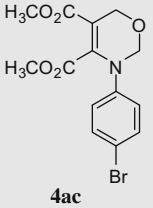
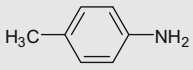
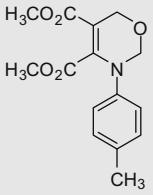
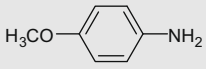
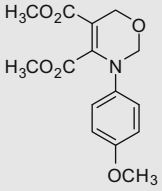
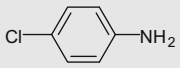
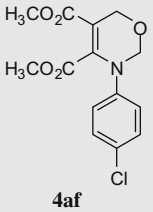
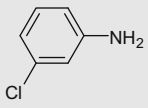
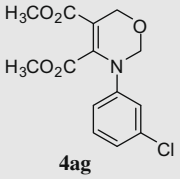
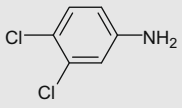
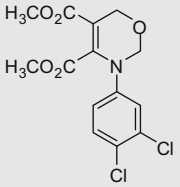
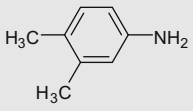
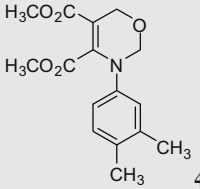
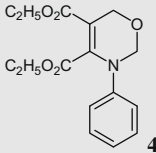
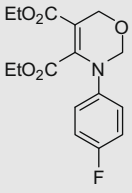
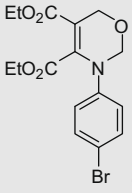
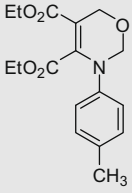
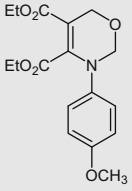
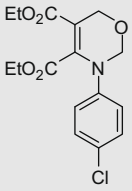
Entry	Alkynoates	Amines	Product	Yield[b] (%)
1	$H_3CO_2C{\equiv}CO_2CH_3$ **1a**	 **2a**	 **4aa**	70
2	**1a**	 **2b**	 **4ab**	80
3	**1a**	 **2c**	 **4ac**	79

Table 2 (*continued*)

Entry	Alkynoates	Amines	Product	Yield[b] (%)
4	**1a**	 **2d**	 **4ad**	74
5	**1a**	 **2e**	 **4ae**	75
6	**1a**	 **2f**	 **4af**	82
7	**1a**	 **2g**	 **4ag**	80
8	**1a**	 **2h**	 **4ah**	84
9	**1a**	 **2i**	 **4ai**	76
10	$EtO_2C{\equiv}CO_2Et$ **1b**	**2a**	 **4ba**	71

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkynoates	Amines	Product	Yield[b] (%)
11	**1b**	**2b**	 **4bb**	78
12	**1b**	**2c**	 **4bc**	77
13	**1b**	**2d**	 **4bd**	72
14	**1b**	**2e**	 **4be**	73
15	**1b**	**2f**	 **4bf**	81

[a] Reaction conditions: dimethyl acetylenedicarboxylate (1.2 mmol), amines (1.0 mmol), formaldehyde (4.0 mmol), HCl (10 mol %).
[b] Determined by GC.

41–58% yields (Table 1, entries 8–12). So the optimized reaction conditions are chosen and shown in entry 2.

On the basis of the above optimization, we proceeded to probe into the scope of the substrates for the formation of 1,3-oxazine (Table 2).[16] It was pleasing to find that all the reactions proceeded rapidly and afforded the desired products in good to excellent yields. For reaction of dimethyl acetylenedicarboxylate **1a**, aniline **2**, and formaldehyde **3**, which are suitable partners in this process similar yields were obtained (Table 2, entries 1–9). This indicates that substituents present on the *p*- and *m*- of aromatic group of aniline have no obvious effects on the reaction. But if we used more sterically hindered *o*-disubstituted amines such as 2,3-difluoro- and 2-methylaniline as substrates, the desired products cannot be formed. When diethyl acetylenedicarboxylate was applied, the solvent methanol should be exchanged to ethanol in order to avoid ester exchange reaction (Table 2, entries 10–15).

In conclusion, we have developed a novel and highly efficient method for the synthesis of 3,4,5-trisubstituted-1,3-oxazine from alkynoates, amines, and formaldehyde with a simple experimental workup procedure, and the target molecules are obtained in good to excellent yields under mild reaction conditions. This domino hydroamination/Prins reaction/cyclization/dehydration sequence proceeded smoothly and rapidly owing to the promotion of Brønsted acids. Further studies and applications on the domino reactions are ongoing in our laboratory, and will be published in due course.

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16. *General procedure*: To a mixture of dimethyl acetylenedicarboxylate **1a** (1 mmol) and aniline **2** (1 mmol), 3 mL methanol was added successively. The mixture was stirred at room temperature for 10 min. Subsequently, hydrochloric acid (10 mmol %) and formaldehyde **3** (3.5 mmol) were added, and the stirring was continued for 5 min. The solution was evaporated to dryness under reduced pressure, and 8 mL of water was added. The aqueous solution was extracted with diethyl ether (3 × 15 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give a pure sample **4aa**.
Dimethyl 3,6-dihydro-3-phenyl-2H-1,3-oxazine-4,5-dicarboxylate (**4aa**): IR (KBr): 3395, 3045, 2858, 1769, 1700, 1457, 1091, 753. ^{1}H NMR (400 MHz, $CDCl_3$):δ = 7.86 (d, 2H, *J* = 8.0 Hz), 7.47 (t, 2H, *J* = 8.0 Hz), 7.31 (t, 1H, *J* = 7.2 Hz), 4.52 (d, 1H, *J* = 10.8 Hz), 4.27 (d, 1H, *J* = 10.0 Hz), 3 4.00 (d, 1H, *J* = 9.2 Hz), 3.89 (d, 1H, *J* = 9.2 Hz), 3.77 (s, 3H), 3.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 166.4, 156.2, 138.3, 129.3, 127.1, 119.5, 72.8, 59.6, 55.1, 53.7, 48.9. MS (EI) *m*/*z*: 277, 247, 200, 119, 91, 77, 59, 45. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.12; H, 5.01; N, 5.10.
Dimethyl 3-(4-fluorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4ab**): IR (KBr): 3397, 3022, 2958, 1773, 1704, 1514, 1009, 835. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.86 (m, 2H), 7.14–7.18 (m, 2H), 4.50 (d, 1H, *J* = 10.4 Hz), 4.24 (d, 1H, *J* = 10.4 Hz), 4.00 (d, 1H, *J* = 9.2 Hz), 3.89 (d, 1H, *J* = 10.4 Hz), 3.78 (s, 3H), 3.33 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 166.2, 156.1, 134.5, 121.5, 121.4, 116.3, 116.1, 59.6, 55.1, 53.7, 49.1. MS (EI) *m*/*z*: 295, 295, 137, 123, 109, 95, 75, 64, 59, 45. Anal. Calcd for $C_{14}H_{14}FNO_5$: C, 56.95; H, 4.78; N, 4.74. Found: C, 56.37; H, 4.82; N, 4.69.
Dimethyl 3-(4-bromophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4ac**): IR (KBr): 3400, 3010, 2925, 1769, 1701, 1491, 1100, 994. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, 2H, *J* = 8.8 Hz), 7.62 (d, 2H, *J* = 9.2 Hz), 4.53 (d, 1H, *J* = 10.4 Hz), 4.27 (d, 1H, *J* = 10.4 Hz), 4.04 (d, 1H, *J* = 8.8 Hz), 3.91–3.94 (d, 1H, *J* = 9.2 Hz), 3.81 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 166.2, 156.1, 137.4, 132.8, 120.9, 120.3, 72.8, 59.6, 55.0, 53.8, 48.8. MS (EI) *m*/*z*: 357, 355, 199, 197, 185, 183, 169, 90, 59, 45. Anal. Calcd for $C_{14}H_{14}BrNO_5$: C, 47.21; H, 3.96; N, 3.93. Found: C, 47.32; H, 4.00; N, 3.84.
Dimethyl 3,6-dihydro-3-p-tolyl-2H-1,3-oxazine-4,5-dicarboxylate (**4ad**): IR (KBr): 3427, 3013, 2918, 1770, 1696, 1510, 1283, 811. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 1H, *J* = 8.4 Hz), 4.49 (d, 1H, *J* = 10.8 Hz), 4.24 (d, 1H, *J* = 10.8 Hz), 3.98 (d, 1H, *J* = 8.8 Hz), 3.89 (d, 1H, *J* = 9.2 Hz), 3.77 (s, 3H), 3.31 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 166.4, 156.1, 137.1, 135.9, 129.8, 119.4, 59.6, 55.1, 53.7, 48.9, 21.1. MS (EI) *m*/*z*: 291, 133, 119, 91, 65, 45. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.79; H, 5.90; N, 4.76.
Dimethyl 3,6-dihydro-3-(4-methoxyphenyl)-2H-1,3-oxazine-4,5-dicarboxylate (**4ae**): IR (KBr):3411, 3014, 2962, 1767, 1695, 1511, 1094, 786. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76–7.80 (m, 2H), 6.95–7.00 (m, 2H), 4.48 (d, 1H, *J* = 10.8 Hz), 4.22 (d, 1H, *J* = 10.8 Hz), 3.98 (d, 1H, *J* = 9.2 Hz), 3.89 (d, 1H, *J* = 8.8 Hz), 3.83 (s, 3H), 3.77 (s, 3H), 3.32 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 166.5, 158.3, 156.0, 131.6, 121.1, 114.4, 72.8, 59.6, 55.6, 55.1, 53.6, 49.1. MS (EI) *m*/*z*: 307, 149, 135, 120, 105, 92, 77, 45. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 57.52; H, 5.61; N, 4.50.
Dimethyl 3-(4-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4af**): IR (KBr): 3400, 3010, 2925, 1769, 1701, 1491, 1100, 994. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, *J* = 8.8 Hz), 7.42 (d, 1H, *J* = 9.2 Hz), 4.48 (d, 1H, *J* = 10.4 Hz), 4.23 (d, 1H, *J* = 10.4 Hz), 3.99 (d, 1H, *J* = 9.2 Hz), 3.88 (d, 1H, *J* = 8.8 Hz), 3.77 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 166.2, 156.1, 136.9, 132.5, 129.4, 120.6, 72.8, 59.6, 55.1, 53.8, 48.8. MS (EI) *m*/*z*: 311, 283, 281, 277, 222, 207, 113, 112, 96, 55.
Dimethyl 3-(3-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4ag**): IR (KBr): 3408, 3008, 2905, 1773, 1711, 1485, 1103, 982. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 7.80–7.82 (d, 1H, *J* = 8.0 Hz), 7.39 (t, 1H, *J* = 8.0 Hz), 7.28 (d, 1H, *J* = 8.0 Hz), 4.48 (d, 1H, *J* = 10.0 Hz), 4.23 (d, 1H, *J* = 10.4 Hz), 3.99 (d, 1H, *J* = 8.8 Hz), 3.87 (d, 1H, *J* = 8.8 Hz), 3.77 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 166.1, 156.1, 139.4, 135.1, 130.3, 127.0, 119.4, 117.4, 72.8, 59.6, 55.0, 53.7, 48.8. MS (EI) *m*/*z*: 311, 283, 281, 224, 222, 168, 113, 111, 75. Anal. Calcd for $C_{14}H_{14}ClNO_5$: C, 53.94; H, 4.53; N, 4.49. Found: C, 53.85; H, 4.56; N, 4.45.
Dimethyl 3-(3,4-dichlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4ah**): IR (KBr): 3409, 3020, 2983, 1766, 1699, 1501, 893. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, 1H, *J* = 1.6 Hz), 7.79 (d, 1H, *J* = 8.8 Hz), 7.51 (d, 1H, *J* = 8.8 Hz), 4.47 (d, 1H, *J* = 10.0 Hz), 4.21 (d, 1H, *J* = 10.4 Hz), 3.99 (d, 1H, *J* = 9.2 Hz), 3.89 (d, 1H, *J* = 8.8 Hz), 3.77 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 166.0, 156.1, 137.7, 133.5, 130.9, 130.7, 120.9, 118.5, 72.8, 59.6, 55.1, 53.8, 48.8. MS (EI) *m*/*z*: 345, 315, 283, 189, 173, 59. Anal. Calcd for $C_{14}H_{13}Cl_2NO_5$: C, 48.58; H, 3.79; N, 4.05. Found: C, 48.66; H, 3.82; N, 3.98.
Dimethyl 3,6-dihydro-3-(3,4-dimethylphenyl)-2H-1,3-oxazine-4,5-dicarboxylate (**4ai**): IR (KBr): 3420, 3031, 2974, 1771, 1703, 1482, 874. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1H), 7.55 (d, 1H, *J* = 10.0 Hz), 7.19 (d, 1H, *J* = 8.4 Hz), 4.46 (d, 1H, *J* = 10.4 Hz), 4.22 (d, 1H, *J* = 10.8 Hz), 3.96 (d, 1H, *J* = 9.2 Hz), 3.88 (d, 1H, *J* = 9.2 Hz), 3.75 (s, 3H), 3.31 (s, 3H), 2.30 (s, 3H), 3.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 166.5, 156.1, 137.7, 136.2, 135.9, 135.8, 130.3, 120.7, 117.1, 72.9, 59.6, 55.2, 53.6, 49.0, 20.1, 19.4. MS (EI) *m*/*z*: 305, 288, 148, 147, 132, 105, 77. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.05; H, 6.23; N, 4.73.
Diethyl 3,6-dihydro-3-phenyl-2H-1,3-oxazine-4,5-dicarboxylate (**4ba**): IR (KBr): 3394, 3014, 2980, 1756, 1692, 1481, 720. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, *J* = 8.4 Hz), 7.43–7.47 (m, 2H), 7.25–7.31 (m, 1H), 4.50 (d, 1H, *J* = 10.4 Hz), 4.18–4.27 (m, 3H), 4.02 (d, 1H, *J* = 8.8 Hz), 3.89 (d, 1H, *J* = 9.2 Hz), 3.43–3.49 (q, 2H, *J* = 7.2 Hz), 1.20–1.23 (t, 3H, *J* = 7.2 Hz), 1.08 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6.165.9, 156.4, 138.4, 129.3, 129.0, 127.1, 125.5, 119.6, 70.8, 67.4, 63.7, 62.3, 55.3, 49.1, 14.7, 13.9. MS (EI) *m*/*z*: 305, 275, 229, 199, 119, 105, 77. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.80; H, 6.31; N, 4.65.
Diethyl 3-(4-fluorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4bb**): IR (KBr): 3453, 3081, 2985, 1703, 1687, 1089, 915. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.78 (m, 2H), 7.05–7.09 (m, 2H), 4.44 (d, 1H, *J* = 10.4 Hz), 4.12–4.19 (m, 3H), 3.97 (d, 1H, *J* = 9.2 Hz), 3.84 (d, 1H, *J* = 9.2 Hz), 3.39 (q, 2H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz), 1.02 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 165.8, 162.1, 159.6, 156.3, 154.1, 70.7, 67.3, 62.9, 55.3, 49.3, 14.6, 13.9. MS (EI) *m*/*z*: 323, 293, 247, 137, 123, 109, 59. Anal. Calcd for $C_{16}H_{18}FNO_5$: C, 59.44; H, 5.61; N, 4.33. Found: C, 59.32 H, 5.57; N, 4.39.
Diethyl 3-(4-bromophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4bc**): IR (KBr): 3409, 2979, 2854, 1769, 1704, 1489, 1224, 1083, 829. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 2H, *J* = 9.2 Hz), 7.59 (d, 2H, *J* = 10.4 Hz), 4.49 (d, 1H, *J* = 10.4 Hz), 4.21–4.25 (m, 3H), 4.03 (d, 1H, *J* = 8.8 Hz), 3.91 (d, 1H, *J* = 9.2 Hz), 3.47 (q, 2H, *J* = 7.2 Hz), 1.25 (t, 3H, *J* = 7.2 Hz), 1.10 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 165.8, 156.3, 137.5, 132.4, 121.0, 120.3, 70.7, 67.4, 63.1, 55.3, 48.9, 30.9, 14.7, 14.0. MS (EI) *m*/*z*: 385, 383, 309, 307, 199, 197, 185, 183, 59. Anal. Calcd for $C_{16}H_{18}BrNO_5$: C, 50.02; H, 4.72; N, 3.65. Found: C, 50.14; H, 4.67; N, 3.70.
Diethyl 3,6-dihydro-3-p-tolyl-2H-1,3-oxazine-4,5-dicarboxylate (**4bd**): IR (KBr): 3421, 2981, 2885, 1752, 1698, 1515, 1089, 818. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, 2H, *J* = 8.4 Hz), 7.24 (d, 1H, *J* = 8.4 Hz), 4.48 (d, 1H, *J* = 10.4 Hz), 4.19–4.24 (m, 3H), 4.01 (d, 1H, *J* = *J* = 8.8 Hz), 3.90 (d, 1H, *J* = 8.8 Hz), 3.45 (q, 2H, *J* = 7.2 Hz), 1.22 (t, 3H, *J* = 7.2 Hz), 1.08 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, CDC_3): δ = 193.6, 166.0, 156.3, 137.0, 136.0, 129.8, 125.6, 119.5, 70.8, 67.4, 62.9, 55.3, 49.1, 21.0, 14.7, 13.9. MS (EI) *m*/*z*: 319, 289, 243, 214, 133, 119, 105, 91, 59. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.06; H, 6.59; N, 4.44.
Diethyl 3,6-dihydro-3-(4-methoxyphenyl)-2H-1,3-oxazine-4,5-dicarboxylate (**4be**): IR (KBr): 3406, 2980, 2879, 1769, 1695, 1611, 1513, 1089, 834. ^{1}H

NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 2H, J = 9.6 Hz), 6.92 (d, 2H, J = 10.0 Hz), 4.42 (d, 1H, J = 10.4 Hz), 4.16–4.20 (m, 3H), 3.97 (d, 1H, J = 9.2 Hz), 3.87 (d, 1H, J = 9.2 Hz), 3.46 (q, 2H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.2 Hz), 1.05 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 166.0, 158.3, 156.2, 131.6, 121.2, 114.4, 70.7, 67.3, 62.8, 55.5, 55.3, 49.3, 14.7, 13.9. MS (EI) m/z: 335, 259, 149, 135, 120, 105, 92, 59. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18; N, 4.39. Found: C, 60.78; H, 6.27; N, 4.21.

Diethyl 3-(4-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate (**4bf**): IR (KBr): 3403, 2983, 2877, 1771, 1734, 1493, 1280, 1088, 855. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81(d, 1H, J = 8.8 Hz), 7.41 (d, 1H, J = 8.8 Hz), 4.49 (d, 1H, J = 10.4 Hz), 4.19–4.24 (m, 3H), 4.03 (d, 1H, J = 8.8 Hz), 3.90 (d, 1H, J = 8.8 Hz), 3.46 (q, 2H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz), 1.08 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 165.8, 156.3, 136.9, 132.4, 129.4, 120.7, 70.8, 67.4, 63.0, 55.3, 49.0. MS (EI) m/z: 339, 309, 263, 236, 153, 139, 59. Anal. Calcd for $C_{16}H_{18}ClNO_5$: C, 56.56; H, 5.34; N, 4.12. Found: C, 56.63; H, 5.37; N, 4.16..