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A highly regioselective tandem 1,3-dipolar cycloaddition of cyclopropene 1,1-diesters and nitrile oxides: synthesis of highly functionalized isoxazoles

Shaojin Chen, Jun Ren, Zhongwen Wang *

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

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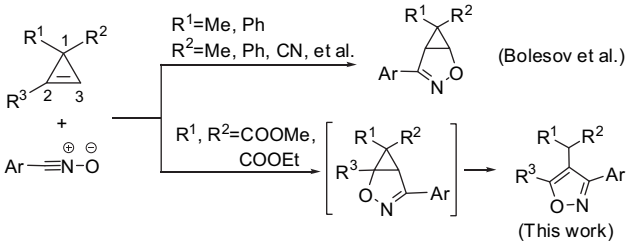
ABSTRACT

A highly regioselective tandem 1,3-dipolar cycloaddition of cyclopropene 1,1-diesters with nitrile oxides was described. This reaction supplied a new method for synthesis of polyfunctionalized isoxazole derivatives in moderate to excellent yields under mild conditions.

1. Introduction

Developing new cycloaddition reactions[1] and tandem[2] reactions of multi-functionalized synthons is one of the most attractive themes in organic synthesis. Cyclopropenes, the readily accessible and the smallest unsaturated carbocycles are an important class of synthons for organic synthesis.[3] One of the most important reaction types of cyclopropenes is the highly strained carbon-carbon double bond-involved cycloadditions, including 1,3-dipolar cycloaddition (1,3-DC) reactions[3g] (e.g., with diazos,[4] carbonyl ylides,[5] azides,[6] nitrile oxides,[7] nitrile imines,[8] and other 1,3-dipoles[9]), Diels–Alder cycloadditions,[10] hetero Diels–Alder cycloadditions,[11] Pauson–Khand reactions,[12] [2+2] cycloadditions[13] and [2+1][14] cycloadditions.[15] Several cycloaddition-based tandem ring-opening reactions of cyclopropenes have also been investigated.[16] We noticed that most of the cyclopropenes applied in the above-mentioned examples are unactivated or being activated by one electron-withdrawing group (EWG) at the sp^3-carbon of the cyclopropene ring. Our attention has been drawn to cyclopropenes activated by two geminal EWGs at the sp^3-carbon of the cyclopropene ring, which easily underwent ring-opening reactions.[17] We wondered that the di-activated cyclopropenes might supply novel cycloaddition-based chemical transformations for organic synthesis. In our research, we found a novel tandem 1,3-DC of a cyclopropene 1,1-diester with a nitrile oxide (generated in situ from hydroximoyl chlorides), which was quite different from that of unactivated cyclopropenes reported by Bolesov et al. (Scheme 1).[7] In our result, a post-tandem ring-opening of cyclopropane ring was involved and an isoxazole heterocycle was obtained. This provided a new method for synthesis of isoxazole derivatives,[18] which are embedded in a number of pharmaceutically important compounds.[19] Herein, we wish to report this tandem reaction. It should be noted that the regioselectivity for the formation of the polysubstituted isoxazoles was excellent.



Scheme 1. Cycloaddition reactions of nitrile oxides with cyclopropenes.

2. Results and discussion

Initially, we examined the reaction of cyclopropene **1a** and 4-chloro-*N*-hydroxybenzimidoyl chloride **2a** in the presence of various bases. While imidazole and potassium *tert*-butoxide were proved to be good bases (Table 1, entries 3–4 and 7–9), Et_3N, DMAP, K_2CO_3 and DBU led to relatively lower yields (Table 1, entries 1, 2, 5

* Corresponding author.
E-mail address: wzwrj@nankai.edu.cn (Z. Wang).

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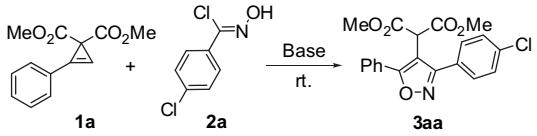
Table 1
Optimization of conditions for the cycloaddition of cyclopropene 1,1-diester **1a** with hydroximoyl chloride **2a** in the present of bases.[a]



Entry	**1a**:**2a** (equiv)	Base (equiv)	Solvent	Time (h)	Yield[c] (%)
1[b]	1:2.8	Et_3N (2)	DCM	87	64
2	1:2.1	DMAP (1.5)	DCM	20	48[d]
3	1:2	Imid. (2.5)	DCM	72	84
4	1:1.4	Imid. (1.5)	DCM	43	88
5	1:1.4	K_2CO_3 (1)	DCM	39	64
6	1:1.4	DBU (1.5)	DCM	115	64
7	1:1.4	KOBut (1.5)	DCM	90	82
8	1:2	KOBut (2)	DCM	72	83
9[b]	1:2.1	KOBut (2.2)	DCM	29	77
10	1:2.7	Imd. (4)	THF	71	44
11	1:2.5	Imid. (3)	DCE	111	80
12	1:2.4	Imid. (2.2)	Et_2O	86	77
13	1:2.1	Imid. (2)	$CHCl_3$	67	70
14	1:2.5	Imid. (3)	Toluene	86	80

[a] Conditions: cyclopropene (0.3 mmol), hydroximoyl chloride (0.42 mmol), base (0.3 mmol) in solvent (5 mL) at room temperature under N_2. More **2a** and base were added until the reaction was completed (monitored by TLC).
[b] **2a** and base were added in one portion, respectively.
[c] Isolated yields.
[d] 43% of **1a** was recovered.

and 6). When **2a** and imidazole were added in portions to a solution of cyclopropene **1a** in dichloromethane (DCM), the best result was obtained and **3aa** was formed in 88% yield. Lower yields were observed in other common solvents (Table 1, entries 10–14).

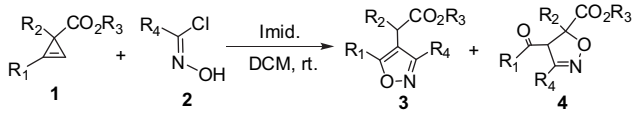
We next evaluated the scope of the reaction by submitting various imidoyl chlorides **2** to the optimized conditions. In general, good results were obtained with *meta*- and *para*-substituted phenyl groups. In contrast, besides the expected product **3**, imidoyl chlorides **2** with *ortho*-substituted phenyl afforded another product **4** (Table 2, entries 4, 10 and 13). Imidoyl chlorides **2** bearing styryl and 2-furyl groups were also competent reactants (Table 2, entries 11 and 15). While aromatic substituents worked well under the standard conditions, *i*-Pr and *n*-Pr substituted reactants **2** (Table 2, entries 5 and 12) failed to achieve satisfying yields.

We next studied the reactions of various cyclopropene 1,1-diesters (**1b**–**1e** and **1g**) with **2b**. While electron-poor phenyl substituted cyclopropene 1,1-diester **1e** performed superbly (Table 2, entry 19), no reaction happened between the *p*-MeO substituent **1g** and **2b** (Table 2, entry 21). Reactions of *n*-butyl-substituted cyclopropene **1b** and unsubstituted cyclopropene **1c** with imidoyl chloride **2b** underwent smoothly to afford the corresponding products **3bb** (Table 2, entry 16) and **3cb** (Table 2, entry 17), respectively. When cyclopropene bearing only one ester group (**1f**) was employed, the tandem reaction also successfully underwent (Table 2, entry 20). A dramatical drop in yield was observed in the reaction of diethyl ester **1d** and imidoyl chloride **2b**, which might be due to the steric effect of the ethyl ester.

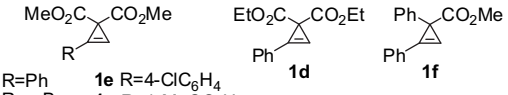
Regioselectivity for these reactions was high, and no other regio-isomers of products **3** or **4** were observed. The structures of **3aa** and **4aj** were characterized by NMR analysis and further confirmed by single-crystal X-ray analysis (Fig. 1).[20]

A plausible mechanism for the formation of isoxazoles **3** and isoxazolines **4** is illustrated in Scheme 2. Highly regioselective 1,3-DC of nitrile oxides **7** and cyclopropene 1,1-diester **1a** afford intermediates **8**, which undergo a push-pull ring-opening process to give intermediates **9**. When R is a hydrogen atom, intermediates **9** can be directly converted to products **3** via an intramolecular hydrogen migration process (path a). When R is not a hydrogen atom,

Table 2
Reactions of various cyclopropenes **1** and nitrile oxide precursors[a]



Cyclopropenes



1a R=Ph **1e** R=4-ClC_6H_4
1b R=*n*-Bu **1g** R=4-$MeOC_6H_4$
1c R=H

Entry	Substrates	R^4	Time (h)	Yield[c] (%)	
				3	**4**
1	**1a**/**2a**	4-ClC_6H_4	43	**3aa** (88)	—
2	**1a**/**2b**	4-$MeOC_6H_4$	43	**3ab** (99)	—
3	**1a**/**2c**	4-MeC_6H_4	96	**3ac** (75)	—
4	**1a**/**2d**	2-ClC_6H_4	68	**3ad** (46)	**4ad** (40)
5[b]	**1a**/**2e**	*i*-Pr	61	**3ae** (23)	—
6	**1a**/**2f**	4-FC_6H_4	55	**3af** (84)	—
7	**1a**/**2g**	Ph	92	**3ag** (99)	—
8	**1a**/**2h**	4-BrC_6H_4	45	**3ah** (71)	—
9	**1a**/**2i**	4-$NO_2C_6H_4$	72	**3ai** (62)	—
10	**1a**/**2j**	1-Naphthyl	67	**3aj** (67)	**4aj** (30)
11	**1a**/**2k**	Styryl	65	**3ak** (74)	—
12[b]	**1a**/**2l**	*n*-Pr	182	**3al** (32)	—
13	**1a**/**2m**	2-BrC_6H_4	42	**3am**(54)	**4am**(41)
14	**1a**/**2n**	3-ClC_6H_4	34	**3an** (78)	—
15	**1a**/**2o**	2-Furyl	39	**3ao** (66)	—
16	**1b**/**2b**	4-$MeOC_6H_4$	72	**3bb** (63)	—
17	**1c**/**2b**	4-$MeOC_6H_4$	37	**3cb** (45)	—
18	**1d**/**2b**	4-$MeOC_6H_4$	42	**3db** (37)	—
19	**1e**/**2b**	4-$MeOC_6H_4$	34	**3eb** (90)	—
20	**1f**/**2b**	4-$MeOC_6H_4$	36	**3fb** (61)	—
21	**1g**/**2b**	4-$MeOC_6H_4$	—	N.R.[d]	

[a] Reaction conditions: **1**:**2**=1:1.4 (equiv), 1.5 equiv of Imid., DCM, rt, N_2. If necessary, more **2** and Imid. were added in portions to complete the reaction.
[b] Et_3N and toluene were used.
[c] Isolated yields.
[d] No reaction.

besides the hydrogen migration process (path a), a competing pathway may happen due to the steric hindrance from the *ortho*-substituent and give **10** and **11** via a C–C and N–O bonds cleavage process (path b), in which the possible mechanism for the reaction of cyclopropenes and nitrones reported by Molchanov can be invoked.[16e] Finally, **10** is trapped by nitrile oxides **7** to give the corresponding 1,3-DC products **4**. Intermediates **10** and **11** were successfully isolated when 2 equiv of **1a** and 1 equiv of nitrile oxide (from **2j**) were employed in the reaction.[21]

3. Conclusions

In conclusion, we have reported a highly regioselective tandem reaction that involves a 1,3-dipolar cycloaddition of cyclopropene 1,1-diesters with nitrile oxides. This provides an efficient method for the synthesis of 3,4,5-trisubstituted isoxazole derivatives. The novel chemistry of the doubly activated cyclopropenes may be extended to other 1,*n*-dipoles. Applications of this tandem reaction, as well as reactions of cyclopropene 1,1-diesters and other 1,*n*-dipoles are under investigation.

4. Experimental section

4.1. General method

All solvents were purchased from commercial sources and were purified according to standard procedures. Reactions were run

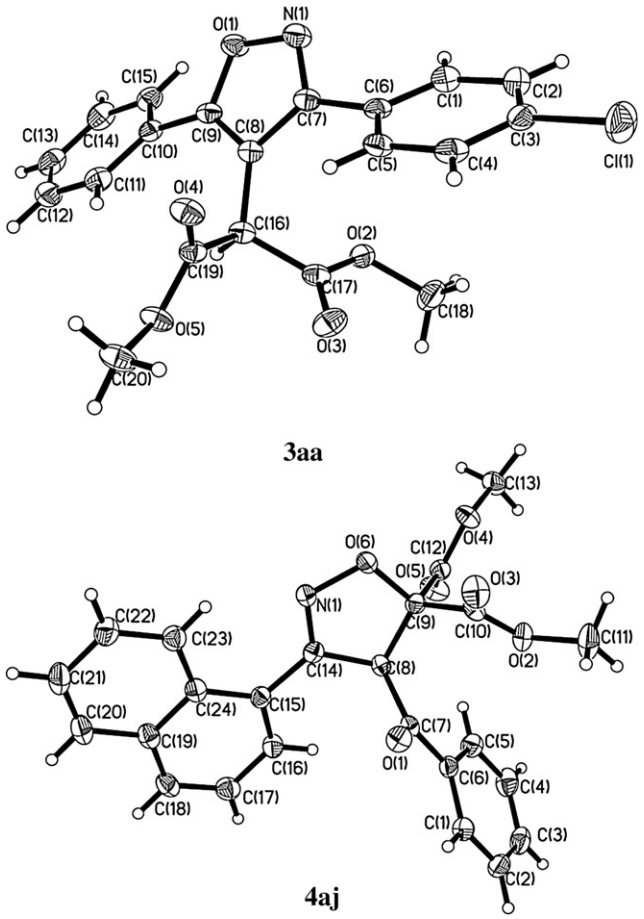
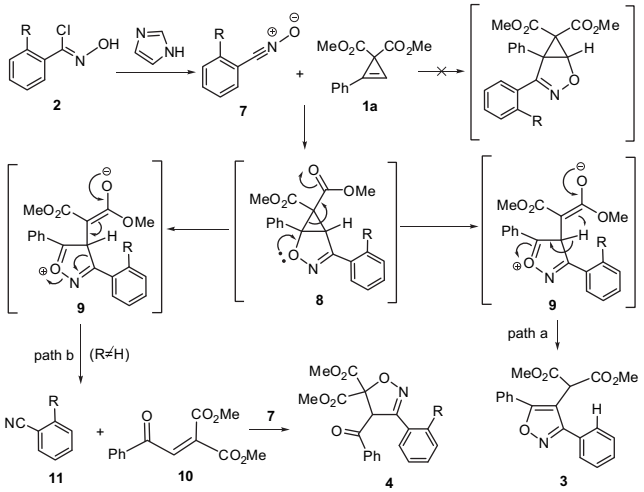


Figure 1. X-ray structure of compounds **3aa** and **4aj**.



Scheme 2. Proposed mechanism for the tandem reaction of cyclopropene 1,1-diester **1a** and nitrile oxides.

under an atmosphere of nitrogen, and visualization was accomplished with UV light (254 nm). Purification of products was carried out by flash chromatography using silica gel (200–300 mesh). All NMR spectra were recorded with a Varian or Bruker spectrometer at 300 MHz or 400 MHz (^{1}H NMR) and 75 MHz or 100 MHz (^{13}C NMR) in $CDCl_3$. Proton nuclear magnetic resonance spectra (^{1}H NMR) are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). High-resolution mass spectra were recorded on an FTMS spectrometer. IR spectra were recorded on a MAGNA-560 spectrometer made by Nicolet Company. Cyclopropenes **1a**–**1g** were prepared according to previously reported procedures.[22] Benzohydroximinoyl chlorides[23] **2o**,[24] **2e**[25] and **2l**[25] were prepared according to literature methods.

4.2. General procedure for the cycloadditions of cyclopropenes 1 and hydroximoyl chlorides 2

Under a positive pressure of nitrogen, to a stirred solution of cyclopropenes **1** (0.3 mmol, 1 equiv) in CH_2Cl_2 (9 mL) were added hydroximoyl chlorides **2** (0.45 mmol, 1.4 equiv) and imidazole (0.3 mmol, 1 equiv), followed by stirring at room temperature. The reaction mixture was monitored by TLC. After 12 h, imidazole (0.15 mmol, 0.5 equiv) was added. If necessary, more hydroximoyl chlorides **2** (0.3 mmol) and imidazole (0.3 mmol) were added in portions. After the completion of the reaction, the solution was concentrated under reduced pressure to afford the crude products **3** (and **4**), which were purified by silica gel column chromatography using petroleum ether and EtOAc (DCM or ether) as eluents.

*4.2.1. 2-[3-(4-Chloro-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3aa**).* White solid, mp: 83–85 °C. Yield: 88%. ^{1}H NMR (400 M, $CDCl_3$): δ 7.67–7.65 (m, 2H), 7.60 (d, J=8.4 Hz, 2H), 7.50–7.48 (m, 3H), 7.44 (d, J=8.4 Hz, 2H), 4.77 (s, 1H), 3.54 (s, 6H). ^{13}C NMR (75 M, $CDCl_3$): δ 169.1, 167.5, 162.7, 136.1, 130.7, 130.4, 128.9, 128.8, 128.0, 127.3, 127.1, 107.0, 52.9, 47.9.HRMS (ESI) calcd for $C_{20}H_{16}ClNO_5$ $(M+Na)^+$: 408.0609, found 408.0604. IR (KBr): ν 3455, 3074, 3008, 2953, 2844, 1758, 1740, 1601, 1491, 1429, 1336, 1287, 1226, 1159, 1132, 1093, 1016, 977, 947, 842, 757 cm^{-1}.

*4.2.2. 2-[3-(4-Methoxy-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3ab**).* White solid, mp: 115–117 °C. Yield: 99%. ^{1}H NMR (400 M, $CDCl_3$): δ 7.69–7.67 (m, 2H), 7.56 (d, J=8.4 Hz, 2H), 7.49–7.48 (m, 3H), 6.99 (d, J=8.4 Hz, 2H), 4.76 (s, 1H), 3.83 (s, 3H), 3.54 (s, 6H). ^{13}C NMR (75 M, $CDCl_3$): δ 168.7, 167.6, 163.4, 160.9, 130.5, 130.3, 128.8, 128.0, 127.4, 120.9, 114.1, 107.1, 55.3, 52.8, 48.1. HRMS (ESI) calcd for $C_{21}H_{19}NO_6$ $(M+Na)^+$: 404.1105, found 404.1099. IR (KBr): ν 3471, 3077, 3006, 2950, 2842, 1744, 1614, 1596, 1493, 1449, 1327, 1287, 1232, 1197, 1164, 1114, 1029, 999, 979, 839, 763 cm^{-1}.

*4.2.3. 2-(5-Phenyl-3-p-tolyl-isoxazol-4-yl)-malonic acid dimethyl ester (**3ac**).* White solid, mp: 105–107 °C. Yield: 75%. ^{1}H NMR (400 M, $CDCl_3$): δ 7.71–7.68 (m, 2H), 7.51–7.48 (m, 5H), 7.28 (d, J=8.0 Hz, 2H), 4.76 (s, 1H), 3.53 (s, 6H), 2.40 (s, 3H). ^{13}C NMR (75 M, $CDCl_3$): δ 168.8, 167.6, 163.7, 139.8, 130.5, 129.4, 128.8, 128.0, 127.4, 125.7, 107.1, 52.8, 48.0, 21.4. HRMS (ESI) calcd for $C_{21}H_{19}NO_5$ $(M+Na)^+$: 388.1155, found 388.1154. IR (KBr): ν 3458, 3070, 3005, 2952, 2847, 1757, 1740, 1615, 1496, 1447, 1336, 1274, 1225, 1193, 1160, 1050, 1018, 978, 946, 837, 777 cm^{-1}.

*4.2.4. 2-[3-(2-Chloro-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3ad**).* Yellow oil. Yield: 46%. ^{1}H NMR (400 M, $CDCl_3$): δ 7.77–7.76 (m, 2H), 7.51–7.49 (m, 5H), 7.42 (t, J=7.6 Hz, 1H), 7.36 (t, J=7.2 Hz, 1H), 4.61 (s, 1H), 3.52 (s, 6H). ^{13}C NMR (75 M, $CDCl_3$): δ 168.8, 167.2, 161.8, 134.1, 132.1, 131.3, 130.6, 129.7, 128.8, 128.0, 127.6, 127.2, 126.8, 107.9, 52.9, 47.6. HRMS (ESI) calcd for $C_{20}H_{16}ClNO_5$ $(M+Na)^+$: 408.0609, found 408.0601. IR (KBr): ν 3474, 3063, 3005, 2953, 2849, 1739, 1622, 1598, 1494, 1435, 1412, 1289, 1239, 1196, 1159, 1076, 1033, 951, 929, 837, 757 cm^{-1}.

*4.2.5. 4-Benzoyl-3-(2-chloro-phenyl)-4H-isoxazole-5,5-dicarboxylic acid dimethyl ester (**4ad**).* Yellowish oil. Yield: 40%. ^{1}H NMR (400 M, $CDCl_3$): δ 7.98 (d, J=7.6 Hz, 2H), 7.62 (d, J=7.4 Hz, 1H), 7.57 (t, J=7.4 Hz, 1H), 7.43 (t, J=7.6 Hz, 2H), 7.27–7.25 (m, 3H), 6.89 (s, 1H), 3.93 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (100 M, $CDCl_3$): δ 193.1, 166.8, 165.4, 155.9, 135.7, 134.4, 132.5, 132.2, 131.6, 130.0, 128.9, 128.8, 127.2, 126.7, 92.3, 62.0, 54.4, 53.3. HRMS (ESI) calcd for $C_{20}H_{16}ClNO_6$

$(M+Na)^+$: 424.0558, found 424.0555. IR (KBr): ν 3479, 3066, 3008, 2956, 2848, 1750, 1683, 1596, 1476, 1449, 1336, 1287, 1217, 1185, 1127, 1080, 1040, 934, 906, 857, 761 cm^{-1}.

*4.2.6. 2-(3-Isopropyl-5-phenyl-isoxazol-4-yl)-malonic acid dimethyl ester (**3ae**).* Yellow oil. Yield: 23%. ^1H NMR (400 M, $CDCl_3$): δ 7.66–7.63 (m, 2H), 7.49–7.48 (m, 3H), 4.78 (s, 1H), 3.72 (s, 6H), 3.07–3.00 (m, 1H), 1.36 (d, J=6.8 Hz, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 168.8, 167.7, 130.3, 128.9, 128.1, 127.4, 106.1, 53.1, 47.3, 26.3, 22.1. HRMS (ESI) calcd for $C_{17}H_{19}NO_5$ $(M+Na)^+$: 340.1155, found 340.1148. IR (KBr): ν 3472, 3063, 2972, 2935, 2873, 1743, 1627, 1597, 1465, 1448, 1312, 1288, 1256, 1196, 1152, 1089, 1029, 959, 929, 880, 760 cm^{-1}.

*4.2.7. 2-[3-(4-Fluoro-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3af**).* White solid, mp: 101–103 °C. Yield: 84%. ^1H NMR (400 M, $CDCl_3$): δ 7.67–7.63 (m, 4H), 7.51 (br, 3H), 7.16 (t, J=8.8 Hz, 2H), 4.77 (s, 1H), 3.55 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 169.0, 167.5, 165.0, 162.9, 162.5, 131.1, 131.0, 130.7, 128.9, 127.9, 127.1, 124.8, 124.7, 115.8, 115.6, 107.0, 52.9, 47.9. HRMS (ESI) calcd for $C_{20}H_{16}FNO_5$ $(M+Na)^+$: 392.0905, found 392.0899. IR (KBr): ν 3453, 3064, 3011, 2955, 2840, 1750, 1735, 1606, 1525, 1430, 1327, 1289, 1237, 1193, 1159, 1139, 1014, 973, 949, 844, 756 cm^{-1}.

*4.2.8. 2-(3,5-Diphenyl-isoxazol-4-yl)-malonic acid dimethyl ester (**3ag**).* White solid, mp: 94–95 °C. Yield: 99%. ^1H NMR (400 M, $CDCl_3$): δ 7.69 (t, J=3.6 Hz, 2H), 7.62 (t, J=2.8 Hz, 2H), 7.50–7.46 (m, 6H), 4.77 (s, 1H), 3.53 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 168.9, 167.6, 163.7, 130.6, 129.8, 129.0, 128.9, 128.6, 128.0, 127.3, 107.1, 52.9, 48.0. HRMS (ESI) calcd for $C_{20}H_{17}NO_5$ $(M+Na)^+$: 374.0999, found 374.1002. IR (KBr): ν 3456, 3056, 2967, 2952, 2851, 1753, 1625, 1574, 1499, 1441, 1328, 1292, 1234, 1202, 1159, 1131, 1019, 977, 946, 834, 750 cm^{-1}.

*4.2.9. 2-[3-(4-Bromo-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3ah**).* White solid, mp: 118–120 °C. Yield: 71%. ^1H NMR (400 M, $CDCl_3$): δ 7.67–7.66 (m, 2H), 7.61 (d, J=8.0 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.51–7.50 (m, 3H), 4.76 (s, 1H), 3.55 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 169.2, 167.5, 162.8, 131.9, 130.7, 130.6, 129.0, 128.0, 127.7, 127.0, 124.4, 107.0, 53.0, 47.9. HRMS (ESI) calcd for $C_{20}H_{16}BrNO_5$ $(M+Na)^+$: 452.0104, found 452.0100. IR (KBr): ν 3471, 3074, 3010, 2952, 2842, 1744, 1620, 1595, 1492, 1448, 1325, 1281, 1229, 1197, 1163, 1105, 1025, 983, 948, 839, 780 cm^{-1}.

*4.2.10. 2-[3-(4-Nitro-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3ai**).* Yellow solid, mp: 96–100 °C. Yield: 62%. ^1H NMR (400 M, $CDCl_3$): δ 8.32 (d, J=8.4 Hz, 2H), 7.89 (d, J=8.4 Hz, 2H), 7.67–7.65 (m, 2H), 7.53 (br, 3H), 4.81 (s, 1H), 3.58 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 169.6, 167.3, 161.9, 148.6, 135.3, 130.9, 130.1, 129.0, 127.9, 126.6, 123.5, 106.9, 53.0, 47.7. HRMS (ESI) calcd for $C_{20}H_{16}N_2O_7$ $(M+Na)^+$: 397.1030, found 397.1025. IR (KBr): ν 3456, 3069, 2956, 2922, 2851, 1757, 1738, 1605, 1526, 1432, 1348, 1290, 1273, 1195, 1160, 1132, 1011, 974, 949, 854, 747 cm^{-1}.

*4.2.11. 2-(3-Naphthalen-1-yl-5-phenyl-isoxazol-4-yl)-malonic acid dimethyl ester (**3aj**).* Yellow oil. Yield: 67%. ^1H NMR (400 M, $CDCl_3$): δ 7.99 (d, J=8.0 Hz, 1H), 7.92 (d, J=7.6 Hz, 1H), 7.83–7.78 (m, 3H), 7.65 (d, J=6.8 Hz, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.55–7.50 (m, 5H), 4.53 (s, 1H), 3.33 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 168.7, 167.4, 162.8, 133.5, 132.1,130.6, 130.3, 128.8, 128.5, 128.3, 128.0, 127.4,126.8, 126.3, 125.5, 125.4, 125.1, 108.7, 52.6, 47.8. HRMS (ESI) calcd for $C_{24}H_{19}NO_5$ $(M+Na)^+$: 424.1155, found 424.1161. IR (KBr): ν 3468, 3058, 3006, 2953, 2845, 1739, 1622, 1594, 1514, 1435, 1324, 1289, 1240, 1196, 1159, 1058, 1025, 979, 942, 805, 733 cm^{-1}.

*4.2.12. 4-Benzoyl-3-naphthalen-1-yl-4H-isoxazole-5,5-dicarboxylic acid dimethyl ester (**4aj**).* Yellow solid, mp: 137–141 °C. Yield: 30%. ^1H NMR (400 M, $CDCl_3$): δ 8.72 (d, J=8.4 Hz, 1H), 7.91 (d, J=8.0 Hz, 2H), 7.81 (d, J=8.4 Hz, 2H), 7.63 (t, J=7.6 Hz, 1H), 7.53 (q, J=7.6 Hz, 2H), 7.41–7.37 (m, 3H), 7.29 (d, J=8.0 Hz, 1H), 6.71 (s, 1H), 3.97 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (100 M, $CDCl_3$): δ 193.4, 167.3, 165.6, 156.4, 135.9, 134.3, 133.8, 131.3, 130.9, 128.9, 128.8, 128.4, 127.8, 127.7, 126.6, 126.1, 124.6, 124.4, 91.3, 63.0, 54.4, 53.4. HRMS (ESI) calcd for $C_{24}H_{19}NO_6$ $(M+Na)^+$: 440.1105, found 440.1099. IR (KBr): ν 3435, 3335, 3042, 2959, 2852, 1773, 1750, 1674, 1594, 1449, 1330, 1290, 1226, 1188, 1137, 1078, 1059, 933, 908, 862, 770 cm^{-1}.

*4.2.13. 2-(5-Phenyl-3-styryl-isoxazol-4-yl)-malonic acid dimethyl ester (**3ak**).* Yellowish solid, mp: 118–120 °C. Yield: 74%. ^1H NMR (400 M, $CDCl_3$): δ 7.69–7.68 (m, 2H), 7.56–7.52 (m, 6H), 7.39 (t, J=7.2 Hz, 2H), 7.33 (d, J=7.2 Hz, 1H), 7.04 (d, J=16.4 Hz, 1H), 4.90 (s, 1H), 3.75 (s, 6H). ^{13}C NMR (75 M, $CDCl_3$): δ 168.5, 167.6, 160.5, 136.2, 135.7, 130.6, 129.1, 128.8, 128.7, 128.0, 127.2, 127.1, 114.4, 106.6, 53.2, 47.5. HRMS (ESI) calcd for $C_{22}H_{19}NO_5$ $(M+Na)^+$: 400.1155, found 400.1151. IR (KBr): ν 3456, 3074, 3033, 2956, 2843, 1763, 1736, 1620, 1498, 1423, 1341, 1242, 1219, 1146, 1115, 1076, 1023, 967, 920, 867, 761 cm^{-1}.

*4.2.14. 2-(5-Phenyl-3-propyl-isoxazol-4-yl)-malonic acid dimethyl ester (**3al**).* Yellow oil. Yield: 32%. ^1H NMR (400 M, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.50–7.48 (m, 3H), 4.78 (s, 1H), 3.73 (s, 6H), 2.67 (t, J=7.8 Hz, 2H), 1.81 (q, J=7.6 Hz, 2H), 1.04 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 M, $CDCl_3$): δ 167.9, 167.6, 163.6, 130.3, 129.0, 128.0, 127.4, 106.8, 53.0, 47.3, 27.6, 20.7, 14.1. HRMS (ESI) calcd for $C_{17}H_{19}NO_5$ $(M+Na)^+$: 340.1155, found 340.1155. IR (KBr): ν 3336, 3064, 2958, 2935, 2874, 1742, 1629, 1598, 1502, 1449, 1380, 1290, 1252, 1196, 1155, 1120, 1030, 961, 930, 837, 757 cm^{-1}.

*4.2.15. 2-[3-(2-Bromo-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3am**).* Yellowish oil. Yield: 54%. ^1H NMR (400 M, $CDCl_3$): δ 7.78–7.77 (m, 2H), 7.70 (d, J=8.0 Hz, 1H), 7.50–7.47 (m, 4H), 7.42 (t, J=7.4 Hz, 1H), 7.35 (t, J=7.8 Hz, 1H), 4.60 (s, 1H), 3.53 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 168.8, 167.2, 163.1, 132.9, 132.1, 131.4, 130.6, 129.7, 129.3, 128.8, 128.0, 127.3, 127.2, 123.7, 107.6, 52.9, 47.7. HRMS (ESI) calcd for $C_{20}H_{16}BrNO_5$ $(M+Na)^+$: 452.0104, found 452.0101. IR (KBr): ν 3473, 3063, 3005, 2953, 2846, 1743, 1698, 1622, 1493, 1447, 1326, 1279, 1237, 1196, 1160, 1072, 1028, 983, 951, 837, 781 cm^{-1}.

*4.2.16. 4-Benzoyl-3-(2-bromo-phenyl)-4H-isoxazole-5,5-dicarboxylic acid dimethyl ester (**4am**).* Yellow oil. Yield: 41%. ^1H NMR (400 M, $CDCl_3$): δ 7.97 (dd, J=8.4 Hz, 1.0 Hz, 2H), 7.57 (tt, J=7.4 Hz, 1.2 Hz, 1H), 7.53 (dd, J=8.4 Hz, 1.6 Hz, 1H), 7.48 (dd, J=8.0 Hz, 1.2 Hz, 1H), 7.43 (t, J=7.8 Hz, 2H), 7.29 (dt, J=8.0 Hz, 1.2 Hz, 1H), 7.21 (dt, J=8.0 Hz, 1.7 Hz, 1H), 6.93 (s, 1H), 3.95 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (100 M, $CDCl_3$): δ 193.1, 166.9, 165.4, 156.8, 135.7, 134.4, 133.0, 132.7, 131.7, 128.9, 128.8, 128.7, 127.8, 121.7, 92.2, 62.1, 54.4, 53.4. HRMS (ESI) calcd for $C_{20}H_{16}BrNO_6$ $(M+Na)^+$: 468.0053, found 468.0049. IR (KBr): ν 3346, 3065, 3008, 2956, 2849, 1778, 1683, 1596, 1472, 1449, 1335, 1286, 1217, 1185, 1162, 1059, 1039, 934, 904, 857, 761 cm^{-1}.

*4.2.17. 2-[3-(3-Chloro-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid dimethyl ester (**3an**).* White solid, mp: 108–110 °C. Yield: 78%. ^1H NMR (400 M, $CDCl_3$): δ 7.70–7.68 (m, 2H), 7.64–7.63 (m, 1H), 7.56–7.51 (m, 4H), 7.48–7.40 (m, 2H), 4.76 (s, 1H), 3.58 (s, 6H). ^{13}C NMR (75 M, $CDCl_3$): δ 169.2, 167.4, 162.5, 134.5, 130.7, 130.5, 129.9, 129.1, 128.9, 128.0, 127.2, 127.1, 107.0, 52.9, 47.9. HRMS (ESI) calcd for $C_{20}H_{16}ClNO_5$ $(M+Na)^+$: 408.0609, found 408.0608. IR (KBr): ν 3456, 3080, 3061, 2962, 2853, 1752, 1735, 1617, 1500, 1418, 1331, 1299, 1278, 1199, 1166, 1083, 1018, 953, 934, 834, 802 cm^{-1}.

*4.2.18. 2-(3-Furan-2-yl-5-phenyl-isoxazol-4-yl)-malonic acid dimethyl ester (**3ao**).* White solid, mp: 85–87 °C. Yield: 66%. ^1H NMR (400 M,

$CDCl_3$): δ 7.68–7.67 (m, 2H), 7.56 (s, 1H), 7.51–7.49 (m, 3H), 7.01 (d, *J*=2.8 Hz, 1H), 6.54 (t, *J*=1.6 Hz, 1H), 5.06 (s, 1H), 3.60 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 169.2, 167.4, 154.6, 144.0, 143.8, 130.7, 128.8, 128.2, 126.9, 111.7, 111.2, 106.2, 52.9, 47.8. HRMS (ESI) calcd for $C_{18}H_{15}NO_6$ $(M+Na)^+$: 364.0792, found 364.0791. IR (KBr): ν 3153, 3061, 3004, 2954, 2847, 1740, 1630, 1595, 1508, 1436, 1323, 1294, 1240, 1197, 1158, 1058, 1014, 981, 932, 835, 779 cm^{-1}.

*4.2.19. 2-[5-Butyl-3-(4-methoxy-phenyl)-isoxazol-4-yl]-malonic acid dimethyl ester (**3bb**).* Yellow oil. Yield: 63%. ^1H NMR (400 M, $CDCl_3$): δ 7.49 (d, *J*=8.0 Hz, 2H), 6.98 (d, *J*=8.4 Hz, 2H), 4.60 (s, 1H), 3.82 (s, 3H), 3.70 (s, 6H), 2.80 (t, *J*=7.4 Hz, 2H), 1.71 (t, *J*=7.2 Hz, 2H), 1.40 (q, *J*=7.2 Hz, 2H), 0.93 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 M, $CDCl_3$): δ 172.8, 167.8, 162.4, 160.7, 130.1, 120.8, 114.3, 105.7, 55.3, 53.0, 46.8, 29.1, 26.4, 22.5, 13.8. HRMS (ESI) calcd for $C_{19}H_{23}NO_6$ $(M+Na)^+$: 384.1418, found 384.1412. IR (KBr): ν 3470, 3003, 2957, 2873, 1742, 1614, 1530, 1460, 1435, 1326, 1296, 1253, 1179, 1155, 1121, 1031, 936, 907, 838, 797 cm^{-1}.

*4.2.20. 2-[3-(4-Methoxy-phenyl)-isoxazol-4-yl]-malonic acid dimethyl ester (**3cb**).* Yellow oil. Yield: 45%. ^1H NMR (400 M, $CDCl_3$): δ 8.73 (s, 1H), 7.51 (d, *J*=8.4 Hz, 2H), 7.00 (d, *J*=8.8 Hz, 2H), 4.62 (s, 1H), 3.84 (s, 3H), 3.75 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 167.6, 161.1, 160.9, 159.1, 130.0, 120.1, 114.5, 110.5, 55.4, 53.4, 46.8. HRMS (ESI) calcd for $C_{15}H_{15}NO_6$ $(M+Na)^+$: 328.0792, found 328.0793. IR (KBr): ν 3458, 3123, 3024, 2959, 2844, 1762, 1735, 1613, 1531, 1460, 1331, 1308, 1286, 1205, 1162, 1123, 1015, 998, 934, 839, 810 cm^{-1}.

*4.2.21. 2-[3-(4-Methoxy-phenyl)-5-phenyl-isoxazol-4-yl]-malonic acid diethyl ester (**3db**).* White solid, mp: 102–105 °C. Yield: 37%. ^1H NMR (400 M, $CDCl_3$): δ 7.75–7.72 (m, 2H), 7.60 (d, *J*=8.4 Hz, 2H), 7.50–7.48 (m, 3H), 6.99 (d, *J*=8.8 Hz, 2H), 4.73 (s, 1H), 4.00 (t, *J*=7.2 Hz, 4H), 3.86 (s, 3H), 1.12 (t, *J*=7.0 Hz, 6H). ^{13}C NMR (75 M, $CDCl_3$): δ 168.7, 167.3, 163.5, 160.8, 130.4, 130.3, 129.0, 128.0, 127.6, 121.0, 114.1, 107.0, 62.2, 55.3, 48.5, 13.8. HRMS (ESI) calcd for $C_{23}H_{23}NO_6$ $(M+Na)^+$: 432.1418, found 432.1415. IR (KBr): ν 3452, 3167, 3077, 2933, 2841, 1749, 1731, 1610, 1572, 1462, 1330, 1296, 1254, 1178, 1135, 1113, 1023, 963, 944, 841, 833 cm^{-1}.

*4.2.22. 2-[5-(4-Chloro-phenyl)-3-(4-methoxy-phenyl)-isoxazol-4-yl]-malonic acid dimethyl ester (**3eb**).* Yellow oil. Yield: 90%. ^1H NMR (400 M, $CDCl_3$): δ 7.66 (d, *J*=8.4 Hz, 2H), 7.53 (d, *J*=8.4 Hz, 2H), 7.46 (d, *J*=8.4 Hz, 2H), 6.98 (d, *J*=8.8 Hz, 2H), 4.73 (s, 1H), 3.82 (s, 3H), 3.56 (s, 6H). ^{13}C NMR (100 M, $CDCl_3$): δ 167.6, 167.5, 163.6, 160.9, 136.7, 130.3, 129.3, 129.1, 125.9, 120.5, 114.2, 107.3, 55.3, 53.0, 47.9. HRMS (ESI) calcd for $C_{21}H_{18}ClNO_6$ $(M+Na)^+$: 438.0715, found 438.0709. IR (KBr): ν 3086, 3005, 2954, 2840, 2255, 1740, 1613, 1576, 1494, 1458, 1328, 1296, 1253, 1196, 1178, 1094, 1049, 984, 948, 837, 770 cm^{-1}.

*4.2.23. [3-(4-Methoxy-phenyl)-5-phenyl-isoxazol-4-yl]-phenyl-acetic acid methyl ester (**3fb**).* Yellow oil. Yield: 61%. ^1H NMR (400 M, $CDCl_3$): δ 7.73 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=4.4 Hz, 2H), 7.43 (s, 3H), 7.32 (s, 2H), 7.26 (s, 3H), 6.96 (d, *J*=8.4 Hz, 2H), 4.49 (s, 1H), 3.87 (s, 3H), 3.46 (s, 3H). ^{13}C NMR (100 M, $CDCl_3$): δ 170.7, 161.5, 158.5, 131.3, 131.2, 130.4, 129.7, 129.5, 128.8, 128.6, 128.2, 121.7, 114.3, 55.4, 53.0, 42.9. HRMS (ESI) calcd for $C_{25}H_{21}NO_4$ $(M+Na)^+$: 422.1363, found 422.1361. IR (KBr): ν 3409, 3052, 2999, 2953, 2837, 1715, 1607, 1515, 1497, 1447, 1302, 1248, 1175, 1116, 1055, 1036, 1025, 971, 922, 863, 782 cm^{-1}.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at: doi:10.1016/j.tet.2009.09.034.

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20. CCDC-727368 (**3aa**) and CCDC-727369 (**4aj**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data.request/cif.
21. Isolation of intermediates **10** and **11**: Under nitrogen atmosphere, to a stirred solution of cyclopropene **1a** (1.5 mmol, 2 equiv) in CH_2Cl_2 (20 mL) were added hydroximoyl chloride **2j** (0.75 mmol, 1 equiv) and imidazole (0.75 mmol, 1 equiv), followed by stirring at room temperature for 13 h. The solution was concentrated under reduced pressure. 1-Naphthonitrile (**11**, 58%) and benzoylmethylenemalonate (**10**, 7%) were isolated by silica gel column chromatography using petroleum ether, DCM and ether as eluents.
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