Efficient conversion of nitronate into nitrile oxide using cyanuric chloride. One-pot synthesis of bicyclic isoxazolines and isoxazoles from nitroalkenes†

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Bicyclic isoxazolines and isoxazoles are obtained in good yields by proceeding through a convenient one-pot, two-step procedure utilizing 2,4,6-trichloro-1,3,5-triazine (TCT) as a dehydrating agent.

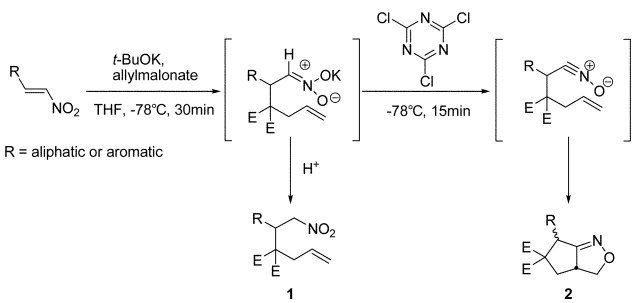
Introduction

Isoxazolines and isoxazoles are often encountered in molecules of medicinal interest. There are numerous examples of these *N*,*O*-heterocycles being used as key building blocks in the total synthesis of several natural and unnatural compounds such as β-lactam antibiotics, quinolizidine and indolizine tricycles, testosterone, sarkomycin, and biotin.[1] The isoxazolines or isoxazoles can also be transformed into a variety of other 1,3-bifunctional organic compounds, whether cyclic or acyclic, such as β-hydroxy ketones, α,β-unsaturated ketones and γ-amino alcohols.[2] Intramolecular 1,3-cycloaddition provides a useful tool for the synthesis of a variety of the above-mentioned heterocyclic compounds, particularly for the construction of merged cyclic ring systems such as bicyclic isoxazolines or isoxazoles. Conventional 1,3-cycloaddition involves a two-step process such as dipolarphile introduction followed by cycloaddition.[3]

The one-pot synthesis of bicyclic isoxazolines proved futile, presumably due to poor conversion of the nitronate into nitrile oxide in the presence of phenyl isocyanate and triethylamine under the conditions usually employed for nitroalkanes.[4] Treatment of the nitronate with di-*tert*-butyl dicarbonate in the presence of catalytic amounts of DMAP led to low to medium yields (24–67%) of the desired isoxazoline in a one-pot procedure, or in separated steps *via* the isolated nitroalkane.[5] A highly stereoselective one-pot synthesis of bicyclic compounds developed by Hassner *et al.* suffers from several drawbacks, such as longer reaction times (15–48 hours), the use of toxic solvent (HMPA), and lower yields (18%) with aliphatic substrates.[5] By adopting a similar procedure, Cheng *et al.* reported that the same reaction with different nucleophiles also suffers from longer reaction times (13 hours).[5] In this context, exploring efficient reagents and the development of simple and mild procedures for the preparation of isoxazolines and isoxazoles is still an interesting topic for organic chemists. Over the past few years, 2,4,6-trichloro-1,3,5-triazine (TCT), also referred as cyanuric chloride, has emerged as an activator or activating agent of carboxylic acids for various organic transformations to afford the corresponding products in good to excellent yields.[6] Our previous study found that nitroalkenes can react with different nucleophiles to generate nitroalkanes, halooximes, nitrile oxides, and/or polycyclic compounds under different reaction conditions or workup procedures.[7] As part of our incessant research efforts with nitroalkene chemistry, we now report a new, economic and efficient dehydrating agent, TCT, for the one-pot synthesis of bicyclic isoxazolines and isoxazoles.

Results and discussion

The methodology is to convert a nitroalkene into the corresponding nitronate by reaction with the allylmalonate anion in THF solution at −78 °C for 30 minutes. Thus, the generated nitronate is transformed into the corresponding nitrile oxide by adding TCT, as the dehydrating agent, directly to the mixture without isolation. The nitrile oxide generated *in situ* undergoes a tandem 1,3-dipolar cycloaddition with the dipolarphile, furnishing the bicyclic isoxazoline within 15 minutes at the same temperature (Scheme 1).



Scheme 1 One-pot and two-step synthesis of isoxazolines.

Preliminary efforts were mainly focused on the evaluation of the optimum amount of TCT at different temperatures. The yields of nitroalkane **1** and isoxazoline **2** obtained by reacting β-nitrostyrene (1.0 eq.) with the potassium dimethyl allylmalonate (1.2 eq.) generated from dimethyl allylmalonate and potassium *t*-butoxide, and subsequent treatment with TCT under different conditions at different temperatures are shown in Table 1.

Initially, the treatment of nitronate solution with 1 eq. of TCT at 0 °C for 15 min afforded nitroalkane **1** and bicyclic isoxazoline **2** in 8% and 61% yields respectively (entry 1). In order to restrict the formation of nitroalkane, we endeavoured to improve the conversion of the nitronate into nitrile oxide by varying the amounts of TCT and/or dimethylaminopyridine (DMAP) in the

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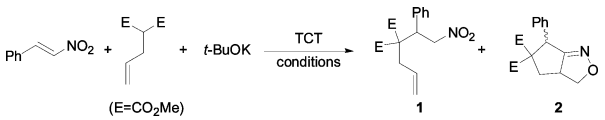
† Electronic supplementary information (ESI) available: General experimental details, characterization data and NMR spectra for all compounds. See DOI: 10.1039/b606717d

Table 1 Reaction of β-nitrostryene with dimethyl allylmalonate and *t*-BuOK, and then with TCT, under different conditions

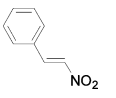
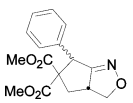
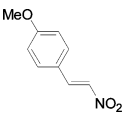
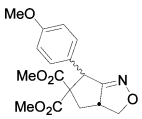
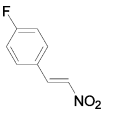
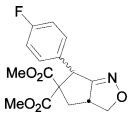
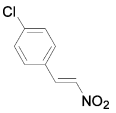
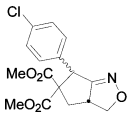
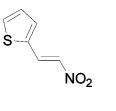
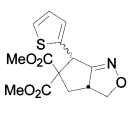
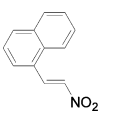
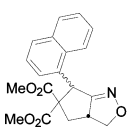


Entry	TCT (eq.)	Additives	Temp (°C)	Yield of **1** (%)[a]	Yield of **2** (%)[a]	*cis* : *trans*[b]
1	1	—	0	8	61	3.2 : 1
2	5	—	0	5	54	3.2 : 1
3	1	DMAP(1 eq.)[c]	0	11	64	4.0 : 1
4	1	—	−78	18	81	4.0 : 1
5	3	—	−78	—	99	4.3 : 1
6	1	$ZnCl_2$ (0.2 eq.)[d]	−78	—	96	3.9 : 1

[a] NMR yield. [b] The *cis* : *trans* ratios were measured by NMR. [c] TCT was initially added to the nitronate solution followed by DMAP. [d] TCT and $ZnCl_2$ were added simultaneously.

reaction system (entries 2 and 3). The product yields were not significantly improved, either by increasing or decreasing the amounts of TCT or DMAP. However, the effect of temperature was apparent. When the reaction was carried out at −78 °C, a mixture of nitroalkane and bicyclic isoxazoline were obtained in quantitative yield (entry 4). The increased product yields at −78 °C imply that the addition of the allylmalonate anion to nitroalkenes should be performed at a lower temperature in order to prevent unwanted reactions such as dimerization of nitrile oxide or the formation of other side products. Although the yield of bicyclic isoxazoline was increased, the reaction still afforded nitroalkane in 18% yield. After considerable experimentation, we were pleased to find that when nitronate was treated with 3 equivalents of TCT at −78 °C, isoxazoline was generated in quantitative yield without any trace of nitroalkane. This result clearly suggests that the use of one eq. of TCT is not enough to completely convert the nitronate into nitrile oxide under these conditions (entry 5). Literature studies revealed that mild Lewis acids such as $ZnCl_2$ can improve the reactivity of TCT.[8] Based on these results, we next investigated the effect of $ZnCl_2$ as an additive. The mild Lewis acidity of zinc chloride dramatically improved the activity of TCT and thus, one eq. of TCT in combination with 0.2 eq. of $ZnCl_2$ was sufficient to afford the nitrile oxide in excellent yield (entry 6). The generality of the TCT or TCT–$ZnCl_2$ system for the one-pot conversion of nitroalkenes into nitrile oxides has been verified using a wide variety of nitroalkenes (Table 2). The bicyclic isoxazolines thus formed (70–97% yield) can be obtained in pure form by simple filtration, followed by passing the crude mixture through a short plug of silica. In some cases the *cis* and *trans* isomers could be further separated by flash column chromatography. In order to extend the scope of this one-pot conversion, dimethylallylmalonate was replaced either with prop-2-ynylmalonates or prop-2-ynylmalononitriles. In both cases the bicyclic products were formed in 62–96% isolated yields. Not only aromatic nitroalkenes, but also aliphatic nitroalkenes in a reaction with these nucleophiles afforded bicyclic products in relatively high yield (73–91%) (Table 3). It is noteworthy to observe that the corresponding aliphatic products were obtained in excellent yield compared to the known methods existing in the literature (entries 6 and 12).[5] The scope of this transformation has been demonstrated by using a wide range of nitroalkenes in which the phenyl group was substituted with different groups. Generally,

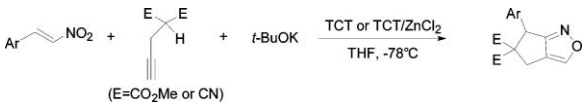
Table 2 The preparation of isoxazoline from nitroalkenes and dimethyl allylmalonate

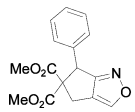
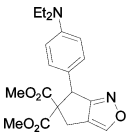
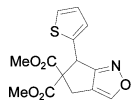
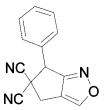
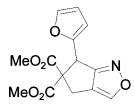
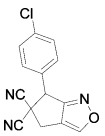
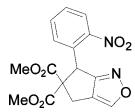
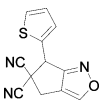
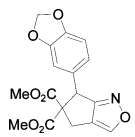
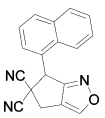
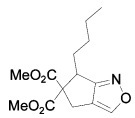
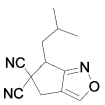
Entry	Nitroalkene	Isoxazoline		% Yield[c](*cis* : *trans*)[d] Method A[a]	Method B[b]
1			**2a**	97(4.3 : 1)	94 (3.9 : 1)
2			**2b**	88(4.3 : 1)	93 (4.5 : 1)
3			**2c**	85(3.4 : 1)	80 (3.8 : 1)
4			**2d**	83(3.7 : 1)	88 (3.4 : 1)
5			**2e**	94(4.5 : 1)	86 (4.8 : 1)
6			**2f**	84(4.1 : 1)	70 (5.0 : 1)

[a] Method A: the reaction was carried out in the presence of 3 eq. of TCT. [b] Method B: the reaction was carried out in the presence of 1 eq. of TCT and 0.2 eq. of $ZnCl_2$. [c] Isolated yields. [d] The *cis* : *trans* ratios were measured by the crude NMR results.

the product yields obtained by reacting nitroalkenes with allylmalonate are higher than those using prop-2-ynylmalonate due to the higher reactivity of the double bond compared to the triple bond (compare entries 1 and 5 of Table 2 to entries 1 and 2 of Table 3). Similarly, the rate of cycloaddition of nitroalkenes with

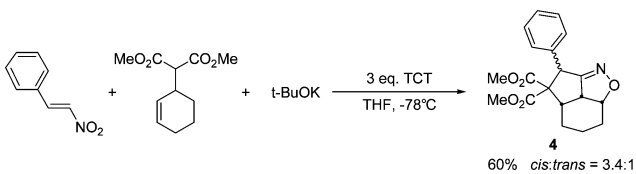
Table 3 Isoxazoles prepared from nitroalkenes and prop-2-ynylmalonate or prop-2-ynylmalononitrile



Entry	Isoxazole		Yield (%)[c] Method A[a]	Method B[b]	Entry	Isoxazole		Yield (%)[c] Method A[a]	Method B[b]
1		**3a**	96	89	7		**3g**	89	81
2		**3b**	88	82	8		**3h**	73	63
3		**3c**	89	82	9		**3i**	78	73
4		**3d**	74	80	10		**3j**	71	66
5		**3e**	91	84	11		**3k**	74	66
6		**3f**	91	84	12		**3l**	86	73

[a] Method A: the reaction was carried out in the presence of 3 eq. of TCT. [b] Method B: the reaction was carried out in the presence of 1 eq. of TCT and 0.2 eq. of $ZnCl_2$. [c] Isolated yield relative to nitroalkene.

prop-2-ynylmalonate is faster than with prop-2-ynylmalononitrile, because the presence of the bulky dimethoxycarbonyl groups enables the dipolarphile to be closer to the nitrile oxide to more easily undergo the intramolecular cycloaddition. That is the reason why the product yields of prop-2-ynylmalonate are always higher than those of prop-2-ynylmalononitrile in a reaction with nitroalkenes (Table 3, compare entries 1–7 to entries 8–12). The same reaction system has been extended efficiently for the construction of a tricyclic ring system. Thus, reaction of β-nitrostyrene with dimethyl 3-cyclohexylmalonate afforded the tricyclic product **4** in 60% isolated yield (Scheme 2).



Scheme 2 Tricyclic isoxazoline prepared from β-nitrostryene and dimethyl-(3-cyclohexyl)malonate.

Conclusions

In conclusion, we have developed a novel procedure for the one-pot synthesis of isoxazolines and isoxazoles, which are often encountered in molecules of medicinal interest. The procedures described here are simple and efficient. The use of TCT as a dehydrating agent has the advantages of being economically viable and more efficient for the conversion of nitronate into nitrile oxide. The reaction system can be successfully applied to a variety of nitroalkenes as well as nucleophiles to synthesize various bicyclic isoxazolines and isoxazoles, and tricyclic products.

Experimental

General

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen when the reactions were sensitive to moisture or oxygen. Solvents were dried over 4 Å molecular sieves. All other commercially available reagents were used as received without purification. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography with E. Merck silica gel 60 (230–400 mesh). MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini-200 or Bruker Avance EX 400 or 500 FT NMR. Elemental analyses were carried out with a HERAEUS VarioEL-III (for CHN). ^{1}H NMR data are reported with the solvent resonance as the internal standard relative to $CDCl_3$–TMS ($\delta = 0.00$) as follows: chemical shift (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constants (J, given in Hz). ^{13}C NMR chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ ($\delta = 77.23$) as internal standard. High-resolution mass spectra (HRMS) are reported as m/z.

Typical experimental procedure

To a stirred solution of *t*-BuOK (168 mg, 1.5 mmol) in 3 mL THF was added a THF solution of dimethyl allylmalonate (159 mg, 1.2 mmol) at −78 °C. After stirring the mixture at −78 °C for 10 minutes, β-nitrostyrene (149 mg, 1.0 mmol) in 5 mL of THF was added dropwise and the mixture stirred for an additional 30 min at the same temperature to generate the nitronate. Then, TCT (564 mg, 3 mmol), or TCT (188 mg, 1 mmol) and $ZnCl_2$ (27 mg, 0.2 mmol) were added sequentially at −78 °C over 15 min. After the addition was complete the reaction mixture was poured into ice cold dilute $HCl_{(aq)}$ solution and then extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 layers were washed with brine and distilled H_2O and dried over anhydrous $MgSO_4$. After evaporation of the organic solvent, the crude product was purified by flash column chromatography using silica gel (eluent; ethyl acetate–hexane; 1 : 5) to obtain bicyclic isoxazoline (**2a**) (294 mg, 97% combined yield).

***cis*-5,5-Dimethoxycarbonyl-6-(4-methoxylphenyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*cis*-2b).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 3462, 3001, 2954, 2840, 2252, 2053, 1731, 1612, 1583, 1515, 1460, 1435, 1362, 1251, 1213, 1180, 1100, 1032, 945, 908, 891, 868, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.20 (m, 2H), 6.84–6.80 (m, 2H), 4.97 (s, 1H), 4.63 (dd, $J = 9.5$, 8.2 Hz, 1H), 4.08 (dd, $J = 12.3$, 8.2 Hz, 1H), 3.90–3.81 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.18 (s, 3H), 2.67 (dd, $J = 13.6$, 11.1 Hz, 1H), 2.54 (dd, $J = 13.6$, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.57, 170.86, 168.79, 159.33, 131.13, 127.40, 113.69, 75.33, 70.17, 55.38, 53.56, 52.53, 51.95, 46.27, 35.16; HRMS (EI) m/z calcd for $C_{17}H_{19}NO_6$ (M^+) 333.1212, found 333.1215.

***trans*-5,5-Dimethoxycarbonyl-6-(4-methoxylphenyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*trans*-2b).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 2950, 1731, 1610, 1514, 1434, 1369, 1278, 1250, 1207, 1179, 1102, 1077, 1031, 836, 788 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.12 (m, 2H), 6.83–6.79 (m, 2H), 4.96 (d, $J = 1.32$ Hz, 1H), 4.67 (dd, $J = 9.6$, 7.7 Hz, 1H), 4.63–4.52 (m, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.12 (s, 3H), 2.85 (dd, $J = 12.9$, 7.6 Hz, 1H), 1.79 (dd, $J = 12.8$, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.29, 171.01, 170.02, 159.26, 129.99, 128.80, 113.89, 75.34, 71.60, 55.50, 55.48, 53.35, 52.49, 45.53, 36.61; HRMS (EI) m/z calcd for $C_{17}H_{19}NO_6$ (M^+) 333.1212, found 333.1215.

***cis*-5,5-Dimethoxycarbonyl-6-(4-fluorophenyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*cis*-2c).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 3445, 2955, 1730, 1606, 1510, 1435, 1365, 1275, 1216, 1161, 1100, 1075, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 2H), 7.02–6.96 (m, 2H), 5.01 (s, 1H), 4.65 (dd, $J = 9.7$, 8.2 Hz, 1H), 4.10 (dd, $J = 12.2$, 8.2 Hz, 1H), 4.13–4.08 (m, 1H), 3.82 (s, 3H), 3.18 (s, 3H), 2.67 (dd, $J = 13.7$, 11.0 Hz, 1H), 2.54 (dd, $J = 13.7$, 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.47, 170.30, 168.72, 162.58 (d, $J = 246$ Hz), 131.84 (d, $J = 8$ Hz), 131.15 (d, $J = 3$ Hz), 115.28 (d, $J = 21$ Hz), 75.50, 70.10, 53.70, 52.61, 51.91, 46.26, 35.25; HRMS (EI) m/z calcd for $C_{16}H_{16}FNO_5$ (M^+) 321.1013, found 321.1014.

***trans*-5,5-Dimethoxycarbonyl-6-(4-fluorophenyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*trans*-2c).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 140–141 °C; IR ($CHCl_3$) ν_{max} 2994, 2950, 2868, 1731, 1605, 1509, 1435, 1279, 1259, 1207, 1174, 1099, 1077, 1012, 849 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.19 (m, 2H), 7.01–6.95 (m, 2H), 4.99 (d, $J = 1.2$ Hz, 1H), 4.68 (dd, $J = 9.6$, 7.8 Hz, 1H), 4.63–4.49 (m, 1H), 3.92 (dd, $J = 12.7$, 7.8 Hz, 1H) 3.81 (s, 3H), 3.12 (s, 3H), 2.85 (dd, $J = 12.8$, 7.6 Hz, 1H), 1.81 (dd, $J = 12.8$, 11.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.91, 170.84, 169.82, 162.43 (d, $J = 246$ Hz), 132.59 (d, $J = 3$ Hz), 130.62 (d, $J = 8$ Hz), 115.42 (d, $J = 21$ Hz), 75.39, 71.63, 55.42, 53.43, 52.48, 45.44, 36.67; HRMS (EI) m/z calcd for $C_{16}H_{16}FNO_5$ (M^+) 321.1013, found 321.1014.

***cis*-5,5-Dimethoxycarbonyl-6-(4-chlorophenyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*cis*-2d).** Purified by column chromatography (ethyl acetate–hexanes 1 : 10) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 3460, 3001, 2954, 1731, 1646, 1596, 1494, 1435, 1415, 1362, 1273, 1213, 1167, 1092, 1016, 942, 908, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 4H), 4.99 (d, $J = 1.04$ Hz, 1H), 4.65 (dd, $J = 9.7$, 8.2 Hz, 1H), 4.10 (dd, $J = 12.2$, 8.2 Hz, 1H), 3.92–3.82 (m, 1H), 3.82 (s, 3H), 3.19 (s, 3H), 2.67 (dd, $J = 13.7$, 10.9 Hz, 1H), 2.55 (dd, $J = 13.7$, 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.40, 170.03, 168.66, 134.19, 133.90, 131.49, 128.54, 75.52, 70.09, 53.74, 52.68, 51.91, 46.37, 35.28; HRMS(EI) m/z calcd for $C_{16}H_{16}ClNO_5$ (M^+) 337.0717, found 337.0716.

***trans*-5,5-Dimethoxycarbonyl-6-(4-chlorophenyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*trans*-2d).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 3463, 3000, 2953, 2869, 1732, 1647, 1595, 1492, 1435, 1412, 1362, 1275, 1258, 1208, 1175, 1090, 1015, 930, 908, 889, 868, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2H), 7.20–7.16 (m, 2H), 4.98

(d, $J = 1.7$ Hz, 1H), 4.68 (dd, $J = 9.6$, 7.8 Hz, 1H), 4.63–4.52 (m, 1H), 3.92 (dd, $J = 12.3$, 7.9 Hz, 1H), 3.81 (s, 3H), 3.13 (s, 3H), 2.85 (ddd, $J = 8.2$, 7.6, 0.4 Hz, 1H), 1.81 (dd, $J = 12.8$, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.78, 170.64, 169.72, 135.30, 133.89, 130.26, 128.65, 75.40, 71.60, 55.41, 53.47, 52.51, 45.53, 36.69; HRMS (EI) m/z calcd for $C_{16}H_{16}ClNO_5$ (M^+) 337.0717, found 337.0716.

***cis*-5,5-Dimethoxycarbonyl-6-(2-thienyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*cis*-2e).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 3108, 3000, 2953, 2879, 1731, 1434, 1361, 1279, 1246, 1208, 1175, 1077, 1042, 943, 905, 886, 864, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, $J = 5.1$, 0.8 Hz, 1H), 7.09 (d, $J = 3.5$ Hz, 1H), 6.95 (dd, $J = 5.1$, 3.5 Hz, 1H), 5.28 (s, 1H), 4.65 (dd, $J = 9.7$, 8.2 Hz, 1H), 4.12 (dd, $J = 12.4$, 8.1 Hz, 1H), 3.91–3.82 (m, 1H), 3.82 (s, 3H), 3.32 (s, 3H), 2.64 (dd, $J = 13.7$, 10.1 Hz, 1H), 2.52 (dd, $J = 13.7$, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.14, 169.88, 168.66, 136.30, 128.52, 126.64, 125.90, 75.83, 70.05, 52.62, 52.81, 51.29, 42.42, 34.56; HRMS (EI) m/z calcd for $C_{14}H_{15}NO_5S$ (M^+) 309.0671, found 309.0670.

***trans*-5,5-Dimethoxycarbonyl-6-(2-thienyl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*trans*-2e).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 3583, 3000, 2953, 2857, 1731, 1434, 1281, 1266, 1208, 1175, 1100, 1077, 1009, 886, 852, 821, 788, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, $J = 4.9$, 1.4 Hz, 1H), 6.94–6.91 (m, 2H), 5.19 (d, $J = 1.6$ Hz, 1H), 4.68 (dd, $J = 9.7$, 7.8 Hz, 1H), 4.63–4.53 (m, 1H), 3.92 (dd, $J = 12.2$, 7.8 Hz, 1H), 3.82 (s, 3H), 3.29 (s, 3H), 2.91 (dd, $J = 13.1$, 7.9 Hz, 1H), 1.86 (dd, $J = 13.1$, 10.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.66, 170.01, 169.51, 138.86, 127.21, 126.93, 125.59, 75.71, 71.20, 54.11, 53.49, 52.83, 41.82, 36.05; HRMS (EI) m/z calcd for $C_{14}H_{15}NO_5S$ (M^+) 309.0671, found 309.0670.

***cis*-5,5-Dimethoxycarbonyl-6-(naphthalen-1-yl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*cis*-2f).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid, which decomposed at 190 °C; IR ($CHCl_3$) ν_{max} 3043, 2994, 2939, 2846, 1750, 1723, 1508, 1448, 1432, 1283, 1247, 1204, 1174, 1166, 1152, 887 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 7.9$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.57–7.53 (m, 1H), 7.49–7.45 (m, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.38–7.37 (m, 1H), 6.06 (s, 1H), 4.69 (dd, $J = 9.5$, 8.4 Hz, 1H), 4.14 (dd, $J = 12.3$, 8.2 Hz, 1H), 4.03–3.81 (m, 1H), 3.85 (s, 3H), 2.82 (t, $J = 13.0$ Hz, 1H), 2.66 (dd, $J = 13.3$, 7.4 Hz, 1H), 2.58 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 172.16, 171.88, 168.15, 133.73, 132.78, 128.78, 128.74, 128.09, 126.50, 125.81, 125.27, 123.81, 75.04, 71.28, 53.88, 52.72, 51.83, 41.12, 36.06; HRMS (EI) m/z calcd for $C_{20}H_{19}NO_5$ (M^+) 353.1263, found 353.1263.

***trans*-5,5-Dimethoxycarbonyl-6-(naphthalen-1-yl)-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*trans*-2f).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 146–148 °C; IR ($CHCl_3$) ν_{max} 3463, 3049, 3002, 2953, 2872, 1732, 1639, 1597, 1511, 1435, 1398, 1361, 1300, 1276, 1255, 1221, 1205, 1103, 1073, 1016, 924, 904, 887, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, $J = 8.6$ Hz, 1H), 7.82 (d, $J = 7.9$ Hz, 1H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.60–7.55 (m, 1H), 7.51–7.47 (m, 1H), 7.36 (t, $J = 7.7$ Hz, 1H), 7.09 (d, $J = 7.2$ Hz, 1H), 5.83 (s, 1H), 4.74 (dd, $J = 9.7$, 8.0 Hz, 1H), 4.69–4.58 (m, 1H), 4.00 (dd, $J = 11.7$, 8.0 Hz, 1H), 3.81 (s, 3H), 3.03 (dd, $J = 12.7$, 7.8 Hz, 1H), 2.61 (s, 3H), 1.85 (dd, $J = 12.7$, 11.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.78, 171.08, 169.79, 134.71, 133.75, 132.54, 128.78, 128.65, 126.74, 126.24, 126.08, 125.13, 124.67, 75.40, 71.60, 56.01, 53.53, 51.89, 41.94, 37.64; HRMS (EI) m/z calcd for $C_{20}H_{19}NO_5$ (M^+) 353.1263, found 353.1263.

5,5-Dimethoxycarbonyl-6-phenyl-4-dihydro-6*H*-cyclopenta[*c*]-isoxazole (3a). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 135–136 °C; IR ($CHCl_3$) ν_{max} 3583, 3461, 3127, 2954, 1753, 1731, 1621, 1497, 1434, 1400, 1281, 1261, 1214, 1162, 1144, 1074, 1048, 941, 898, 863, 819 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.30–7.20 (m, 3H), 7.19–7.16 (m, 2H), 5.32 (s, 1H), 3.80 (s, 3H), 3.72 (dd, $J = 16.6$, 1.4 Hz, 1H), 3.21 (s, 3H), 3.14 (dd, $J = 16.6$, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 171.13, 168.81, 150.43, 136.16, 129.06, 128.56, 128.21, 121.39, 73.01, 53.51, 52.53, 48.72, 29.70; HRMS (EI) m/z calcd for $C_{16}H_{15}NO_5$ (M^+) 301.0950, found 301.0955.

5,5-Dimethoxycarbonyl-6-(2-thienyl)-4-dihydro-6*H*-cyclopenta-[*c*]isoxazole (3b). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 129–130 °C; IR ($CHCl_3$) ν_{max} 3439, 3109, 2954, 2785, 1732, 1626, 1433, 1409, 1271, 1214, 1174, 1116, 1065, 941, 888, 853, 823, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.23–7.21 (m, 1H), 6.94–6.91 (m, 2H), 5.53 (s, 1H), 3.81 (s, 3H), 3.68 (dd, $J = 16.5$, 1.2 Hz, 1H), 3.41 (s, 3H), 3.14 (dd, $J = 16.5$, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 170.71, 168.55, 150.62, 137.44, 127.55, 126.82, 125.89, 120.66, 72.88, 53.54, 52.84, 44.07, 29.26; HRMS (EI) m/z calcd for $C_{14}H_{13}NO_5S$ (M^+) 307.0514, found 307.0513.

5,5-Dimethoxycarbonyl-6-(2-furyl)-4-dihydro-6*H*-cyclopenta-[*c*]isoxazole (3c). Purified by column chromatography (ethyl acetate–hexanes 1 : 10) after concentration *in vacuo* to give a white solid which decompose at 134 °C; IR ($CHCl_3$) ν_{max} 3126, 2956, 2774, 1732, 1624, 1499, 1448, 1434, 1400, 1274, 1257, 1216, 1163, 1144, 1069, 1045, 1013, 931, 885, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.33–7.32 (m, 1H), 6.30–6.29 (m, 1H), 6.21 (d, $J = 3.2$ Hz, 1H), 5.38 (s, 1H), 3.80 (s, 3H), 3.73 (dd, $J = 16.4$, 1.1 Hz, 1H), 3.49 (s, 3H), 3.15 (dd, $J = 16.4$, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.54, 169.89, 168.51, 150.55, 149.25, 143.02, 120.92, 110.69, 109.22, 71.57, 53.63, 53.12, 42.74, 29.54; HRMS (EI) m/z calcd for $C_{14}H_{13}NO_6$ (M^+) 291.0743, found 291.0746.

5,5-Dimethoxycarbonyl-6-(2-nitrophenyl)-4-dihydro-6*H*-cyclopenta[*c*]isoxazole (3d). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 134–135 °C; IR ($CHCl_3$) 3126, 2957, 1736, 1627, 1531, 1435, 1408, 1356, 1274, 1214, 1168, 1067, 944, 900, 864, 848, 824, 786 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.89 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.50–7.41 (m, 2H), 7.02 (d, $J = 7.5$ Hz, 1H), 6.26 (s, 1H), 3.78 (s, 3H), 3.76 (d, $J = 16.8$ Hz, 1H), 3.28 (s, 3H), 3.21 (dd, $J = 16.8$, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.56, 170.32, 168.47, 150.95, 150.38, 132.83, 131.02, 130.65, 129.15, 125.12,

121.55, 72.92, 53.80, 52.94, 42.49, 29.97; HRMS (EI) m/z calcd for $C_{16}H_{14}N_2O_7$ (M^+) 346.0800, found 346.0813.

5,5-Dimethoxycarbonyl-6-(1,3-benzodioxol-5-yl)-4-dihydro-6*H*-cyclopenta[*c*]isoxazole (3e). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 93–94 °C; IR ($CHCl_3$) ν_{max} 3115, 2955, 2780, 1732, 1627, 1504, 1489, 1444, 1408, 1364, 1267, 1216, 1066, 1038, 931, 881, 825, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 6.72–6.66 (m, 3H), 5.91–5.90 (m, 2H), 5.23 (s, 1H), 3.79 (s, 3H), 3.66 (dd, J = 18.1, 1.0 Hz, 1H), 3.33 (s, 3H), 3.11 (dd, J = 16.5, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.91, 170.96, 168.70, 150.45, 147.69, 147.37, 129.49, 122.49, 121.16, 109.38, 108.15, 101.22, 72.74, 53.38, 52.58, 48.31, 29.46; HRMS (EI) m/z calcd for $C_{17}H_{15}NO_7$ (M^+) 345.0849, found 345.0847.

5,5-Dimethoxycarbonyl-6-(*n*-butyl)-4-dihydro-6*H*-cyclopenta-[*c*]isoxazole (3f). Purified by column chromatography (ethyl acetate–hexanes 1 : 10) after concentration *in vacuo* to give a white solid with a melting point of 63–64 °C; IR ($CHCl_3$) ν_{max} 3583, 3461, 2956, 2863, 1735, 1629, 1454, 1435, 1401, 1268, 1215, 1163, 1119, 1066, 954, 938, 872, 835, 820, 792, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 3.86 (dd, J = 11.3, 3.9 Hz, 1H), 3.762 (s, 3H), 3.760 (s, 3H) 3.48 (dd, J = 16.4, 1.3 Hz, 1H), 3.09 (dd, J = 16.4, 1.3 Hz, 1H), 1.69–1.25 (m, 6H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.51, 171.20, 169.65, 149.54, 120.06, 70.40, 53.37, 52.92, 43.43, 29.56, 29.45, 28.98, 22.63, 12.06; HRMS (EI) m/z calcd for $C_{14}H_{19}NO_5$ (M^+) 281.1263, found 281.1258.

5,5-Dimethoxycarbonyl-6-(4-diethylaminophenyl)-4-dihydro-6*H*-cyclopenta[*c*]isoxazole (3g). Purified by column chromatography (methanol–chloroform 1 : 50) after concentration *in vacuo* to give a white solid with a melting point of 104–106 °C; IR ($CHCl_3$) ν_{max} 3668, 3451, 2953, 2291, 1793, 1733, 1613, 1521, 1457, 1435, 1372, 1269, 1163, 1147, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.05–6.95 (m, 2H), 6.62–6.57 (m, 2H), 5.21 (s, 1H), 3.79 (s, 3H), 3.69 (dd, J = 16.5, 1.3 Hz, 1H), 3.35–3.27 (m, 4H), 3.29 (s, 3H), 3.10 (dd, J = 16.5, 1.3 Hz, 1H), 1.11 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.42, 171.19, 168.86, 149.95, 147.39, 129.63, 122.03, 121.67, 111.69, 72.71, 53.16, 52.37, 47.96, 44.30, 29.29, 12.44; HRMS (EI) m/z calcd for $C_{20}H_{24}N_2O_5$ (M^+) 372.1685, found 372.1691.

5,5-Dinitrile-6-phenyl-4-dihydro-6*H*-cyclopenta[*c*]isoxazole (3h). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 143–144 °C; IR ($CHCl_3$) ν_{max} 3583, 3137, 2923, 1708, 1630,1499, 1455, 1406, 1261, 1070,950, 847, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.48 (s, 5H), 5.04 (s, 1H), 3.70 (d, J = 15.7 Hz, 1H), 3.58 (dd, J = 15.7, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.48, 152.65, 131.05, 130.36, 129.65, 128.86, 118.56, 114.51, 113.33, 53.59, 48.30, 34.53; HRMS (EI) m/z calcd for $C_{14}H_9N_3O$ (M^+) 235.0746, found 235.0746.

5,5-Dinitrile-6-(4-chlorophenyl)-4-dihydro-6*H*-cyclopenta[*c*]-isoxazole (3i). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 108–109 °C; IR ($CHCl_3$) ν_{max} 3479, 3139, 3003, 2920, 2252, 2126, 1911, 1710, 1630, 1597, 1577, 1494, 1446, 1405, 1362, 1296, 1260, 1224, 1112, 1092, 1071, 1016, 950, 903, 867, 833, 806, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.43–7.49 (m, 4H), 5.02 (s, 1H), 3.71 (d, J = 15.7 Hz, 1H), 3.58 (dd, J = 15.7, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.09, 152.85, 136.63, 130.25, 129.94, 129.42, 118.47, 114.21, 113.22, 52.99, 48.24, 34.50; HRMS (EI) m/z calcd for $C_{14}H_8ClN_3O$ (M^+) 269.0356, found 269.0357.

5,5-Dinitrile-6-(2-thienyl)-4-dihydro-6*H*-cyclopenta[*c*]isoxazole (3j). Purified by column chromatography (ethyl acetate–hexanes 1 : 10) after concentration *in vacuo* to give a white solid with a melting point of 129–130 °C; IR ($CHCl_3$) ν_{max} 3583, 3115, 2923, 2774, 2252, 1728, 1709, 1630, 1509, 1444, 1408, 1365, 1296, 1237, 1120, 1070, 1043, 947, 856, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.44 (dd, J = 5.1, 0.7 Hz, 1H), 7.33 (d, J = 3.7 Hz, 1H), 7.12 (dd, J = 5.1, 3.7 Hz, 1H), 5.31 (s, 1H), 3.71 (d, J = 15.7, 1H), 3.57 (dd, J = 15.7, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.49, 152.86, 132.36, 129.25, 128.03, 127.94, 118.01, 114.28, 113.03, 49.18, 48.78, 34.23; HRMS (EI) m/z calcd for $C_{12}H_7N_3OS$ (M^+) 241.0310, found 241.0313.

5,5-Dinitrile-6-(naphthalen-1-yl)-4-dihydro-6*H*-cyclopenta[*c*]-isoxazole (3k). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with the melting point of 180–181 °C; IR ($CHCl_3$) ν_{max} 3583, 3137, 3054, 2939, 1709, 1630, 1598, 1514, 1443, 1409, 1360, 1293, 1223, 1071, 949, 803, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 2H) 7.72–7.68 (m, 1H), 7.63–7.59 (m, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 7.1 Hz, 1H), 5.98 (s, 1H), 3.78–3.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.04, 152.72, 134.24, 131.73, 131.04, 129.67, 128.03, 127.72, 127.52, 126.83, 125.51, 122.45, 118.96, 115.22, 113.21, 48.81, 47.26, 35.18; HRMS (EI) m/z calcd for $C_{18}H_{11}N_3O$ (M^+) 285.0902, found 285.0902.

5,5-Dinitrile-6-(*iso*-butyl)-4-dihydro-6*H*-cyclopenta[*c*]isoxazole (3l). Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a colorless oil; IR ($CHCl_3$) ν_{max} 2960, 2923, 2873, 2247, 1706, 1630, 1506, 1469, 1445, 1403, 1370, 1305, 1278, 1220, 1168, 1069, 943, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 3.82 (dd, J = 9.4, 6.4 Hz, 1H), 3.59 (dd, J = 15.7, 0.6 Hz, 1H), 3.48 (dd, J = 15.7, 1.4 Hz, 1H), 2.08–2.18 (m, 1H), 1.97 (ddd, J = 13.7, 9.3, 6.2 Hz, 1H), 1.84 (ddd, J = 13.7, 8.3, 6.2 Hz, 1H), 1.09 (d, J = 6.4 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.02, 151.68, 117.52, 114.79, 113.49, 46.07, 44.91, 38.45, 34.73, 25.79, 22.91, 22.02; HRMS (EI) m/z calcd for $C_{12}H_{13}N_3O$ (M^+) 215.1059, found 215.1060.

***cis*-4,4-Dimethoxycarbonyl-3-phenyl-4a,5,6,7,7a,7b-hexahydro-3*H*-indeno[1,7-*cd*]isoxazole (*cis*-4).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with the melting point of 189–190 °C; IR ($CHCl_3$) ν_{max} 3032, 2952, 2864, 1729, 1645, 1497, 1455, 1435, 1355, 1313, 1280, 1254, 1205, 1180, 1079, 1044 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.23 (m, 5H), 5.02 (s, 1H), 4.81 (dd, J = 17.2, 8.8 Hz, 1H), 3.84 (s, 3H), 3.77 (dd, J = 9.2, 8.2 Hz, 1H), 3.26 (s, 3H), 2.99–2.92 (m, 1H), 2.27–2.24 (m, 1H), 2.18–2.13 (m, 1H), 1.74–1.70 (m, 1H), 1.61–1.41 (m, 2H), 1.02–0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.91, 169.77, 166.70, 135.65,

129.94, 127.99, 127.57, 75.66, 74.20, 54.22, 53.48, 51.54, 46.57, 41.90, 29.02, 25.43, 19.78; HRMS (EI) m/z calcd for $C_{19}H_{21}NO_5$ (M^+) 343.1420, found 303.1109; Elemental analysis calculated for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16: N, 4.08. Found: C, 66.40; H, 6.15; N, 3.93%.

***trans*-4,4-Dimethoxycarbonyl-3-phenyl-4a,5,6,7,7a,7b-hexahydro-3*H*-indeno[1,7-*cd*]isoxazole (*trans*-4).** Purified by column chromatography (ethyl acetate–hexanes 1 : 5) after concentration *in vacuo* to give a white solid with a melting point of 154–155 °C; IR ($CHCl_3$) ν_{max} 3032, 2954, 1730, 1644, 1601, 1497, 1456, 1435, 1280, 1254, 1207, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.21 (m, 5H), 5.05 (d, $J = 2.0$ Hz, 1H), 4.85 (dd, $J = 17.2$, 8.8 Hz, 1H), 4.60 (dd, $J = 8.6$, 8.2 Hz, 1H), 3.79 (s, 3H), 3.00 (s, 3H), 2.95–2.90 (m, 1H), 2.11–2.06 (m, 1H), 1.69–1.63 (m, 2H), 1.39–1.29 (m, 1H), 1.08–0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.24, 169.81, 169.41, 135.63, 128.75, 128.28, 127.64, 77.02, 56.99, 52.64, 52.01, 44.71, 40.51, 28.49, 24.28, 20.28; HRMS (EI) m/z calcd for $C_{19}H_{21}NO_5$ (M^+) 343.1420, found 303.1109; Elemental analysis calculated for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16: N, 4.08. Found: C, 66.41; H, 6.15; N, 3.93%.

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