Journal of Molecular Structure 1060 (2014) 223–232

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

NMR studies on [2+3] cycloaddition of nitrile oxides to cyclohexene derivatives

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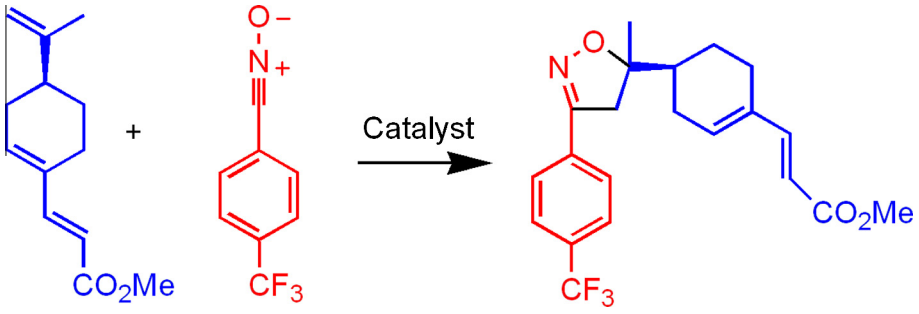
HIGHLIGHTS

- Site selectivity and regioselectivity of the [2+3] cycloaddition reaction was established by 2D NMR spectroscopy.
- Outstanding effect of carbohydrate-ytterbium triflate catalysts on selectivity of the reaction was demonstrated.
- Influence of alkene electron densities on cycloaddition to cyclohexene derivatives was found.
- Complete ^{1}H and ^{13}C NMR characterization of 3a,4,5,6,7,7a-hexahydro-1,2-benzoxazoles was achieved.

GRAPHICAL ABSTRACT

[2+3] Cycloaddition of nitrile oxides to conjugated ester substituted with 2-propenyl group occurs with a complete site selectivity and regioselectivity.



ARTICLE INFO

Article history:
Received 9 October 2013
Received in revised form 5 December 2013
Accepted 5 December 2013
Available online 22 December 2013

Keywords:
[2+3] Dipolar cycloaddition
Cyclohexenes
Site selectivity
2D NMR

ABSTRACT

Site selectivity, regioselectivity and stereoselectivity of [2+3] cycloaddition of 4-trifluoromethylbenzonitrile oxide to cyclohexene carboxylates substituted with alkenyl functions were examined. Site selectivity was correlated with electron charges of alkenyl carbon atoms. Structure of the products has been established by an extensive application of 2D ^{1}H and ^{13}C NMR spectroscopy and electrospray ionization mass spectrometry.

1. Introduction

[2+3] Cycloaddition of nitrile oxides to alkenes is the most convenient method for the preparation of 2-isoxazolines [1] which can be easily reduced to several synthetically important compounds such as β-hydroxy ketones, β-hydroxy esters, α,β-unsaturated carbonyl compounds or iminoketones [2].

The nitrile oxides can be formed either by Huisgen method from aldoximes by chlorination and base-induced dehydrochlorination [1] or by dehydration of primary nitro compounds by phenyl isocyanates [3] (Mukayama method) or ethyl chloroformate (Shimizu method) [4].

Reactions of monosubstituted and 1,1-disubstituted alkenes are very regioselective favoring strongly 5-substituted 2-isoxazolines. On the other hand 1,2-disubstituted olefins usually afford mixtures of regio- and stereoisomers. Two methods have been used to solve these problems. One approach was a substrate control, an application of optically active reagents, much more often of

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http://dx.doi.org/10.1016/j.molstruc.2013.12.035

dipolarophiles than dipoles. One variant of this method was the use of chiral auxiliaries temporarily linked usually by an ester or amide bond to the dipolarophiles [5]. The second more effective approach relied on chiral metal reagents and catalysts. Shortage of reports on metal assisted 1,3-dipolar cycloadditions of nitrile oxides was due to interference of catalyst with generation of these dipoles and formation of unreactive complexes [6]. First asymmetric metal-catalyzed [2+3] cycloaddition reactions of nitrile oxides to γ-substituted allylic alcohols were carried out with diethylzinc as a catalyst, and (*R,R*)-diisopropyl tartrate as the chiral auxiliary [7]. An expedient approach to achieve an excellent regio- and enantioselectivity was a modification of the dipolarophile by attaching an achiral template of pyrazolidinone type and use of a bulky chiral Lewis acid obtained from magnesium iodide and bis-oxazoline derivative. [8] The diastereoselectivity of the thermal and magnesium-mediated cycloaddition of substituted nitrile oxides with chiral homoallylic alcohols, where anti product was favored, was explored using density functional theory [9].

Other catalytic systems applied involved acrylamides bearing chiral auxiliary of oxazolidinone and imidazolidinone type and a chiral complex comprising ytterbium triflate and 2,6-bis[4-(*S*)-isopropyl-2-oxazolidin-2-yl]pyridine (PyBOX) ligand. [10]. Excellent enantioselectivities with moderate to good regioselectivities were achieved in cycloaddition reaction of aryl nitrile oxides and crotonamides with complexes of carbohydrates with $Yb(OTf)_3$, $TiCl_4$, $Mg(OTf)_2$, and CsF as well as with (−)-sparteine-$Yb(OTf)_3$ system. High enantiomeric excess and high regioselectivity were observed for cinnamides in reactions mediated by $Yb(OTf)_3$ complexes with carbohydrates, *R*-BINOL, and (−)-sparteine [11]. Asymmetric cycloaddition reactions of nitrile oxides catalyzed by chiral binaphthyldiimine-Ni(II) complexes displayed high regioselectivity and moderate to high enantioselectivity. Molecular modeling using PM3 calculations were carried out to gain insight into the mechanisms of the asymmetric induction [12].

Site-selectivity of nitrile oxides cycloaddition to polyunsaturated alkenes was examined in several laboratories. In cycloaddition of benzonitrile oxide to 2-alkoxy-1,3-butadienes only the unsubstituted vinyl group participated in the reactions while in case of phenylglyoxylonitrile oxide both double bonds reacted [13]. This result indicated the dominance of steric effect over the electronic one in the first case, where more sterically demanding dipole did not interact with the activated double bond. In reactions of nitrile oxides with dimethyl 7-(diphenylmethylene)bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate only disubstitured norbornene double bond partcipated [14]. Similarly in recently examined cycloadditions of aryl nitrile oxides to norbornenes substituted with an acrylate-derived moiety only adducts to norbornene system were formed with good site and *exo* selectivity [15].

[2+3] Cycloaddition of nitrile oxides to some cycloalkenes was examined before. Cycloadditions to cyclobutene, cyclopentene, and to 2,5-dihydrofuran derivatives were described in the review literature [2]. Cycloaddition reaction of nitrile oxides derived from aromatic aldoximes to unsubstituted cycloalkenes (cyclopentene, cyclohexene, cycloheptene and cyclooctene) provided only cis-fused cycloadducts [16]. The cycloaddition of different nitrile oxides to (*R*)-(+)-limonene, proceeded regioselectively and not stereospecifically at the extracyclic double bond, to form (5*R*/*S*)-isoxazolines [17].

Herein we present results of our research concerning site selectivity, regioselectivity and stereoselectivity of 1,3-dipolar cycloaddition of 4-trifluoromethylbenzonitrile oxide to cyclohexene carboxylates and to cyclohexenes functionalized with alkenyl and alkenoate substituents. Structure of the products has been established by an extensive application of 2D ^1H and ^{13}C NMR spectroscopy and electrospray ionization mass spectrometry. Some of the obtained products showed fungicidal activities.

2. Experimental

2.1. Materials and physical measurements

Reagent-grade chemicals were used without further purification unless otherwise noted. Acids **1**, **7** and aldehydes **10**, **16** were purchased from Aldrich. Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and *N*-chlorosuccinimide (NCS) in *N,N*-dimethylformamide (DMF) [18].

Spectra were recorded as follows: IR spectra on a JASCO FTIR-420 spectrometer, ^1H, ^{13}C NMR, COSY (correlation spectroscopy), HSQC (heteronuclear single quantum coherence), HMBC (heteronuclear multiple bond correlation) and NOESY (nuclear Overhauser effect spectroscopy) analyses on a Varian 500 UNITY plus-500 and a Varian VNMRS 600 spectrometers in deuterated chloroform or acetone. The ^1H NMR spectra were recorded using single-pulse sequence and spectral width (SW) ca. 7000 Hz, 30° pulse width (pw = 2.3 ms), an acquisition time (at) of ca. 3.2 s and 22 k complex points. The FIDs were processed with zero filling. The ^{13}C spectra were obtained using a spectral range of ca. 38000 Hz, 30° pulse width (4.2 ms), an acquisition time of ca. 1.2 s and a relaxation delay of 1.0 s and collecting 48 k complex points. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard, coupling constants are reported in Hz. The 2D g-COSY and NOESY spectra were run using spectral width (ca. 6500 Hz) in both dimensions, at = 0.25 s, 2–4 (COSY) and 4–8 (NOESY) transients per 256 increments, relaxation delay d1 = 1.0 s. Prior to Fourier transormation (FT) the data were processed using squared sinebell (COSY) and gaussian (NOESY) multiple function. In case of the NOESY experiments mixing time ca. 500–700 ms was chosen. The echo-antiecho phase-sensitive, gradient selected $^1H/^{13}C$ HSQC correlation were obtained with an acquisition time (at) of 0.25 s, spectral window of 6500 Hz (F2) and 24,000 Hz (F1), 2×512 increments in the ^{13}C dimension, a d1 = 1.0 s relaxation delay and 2 transients per t_1 increment. Experiments were optimized for $^1J(C—H) = 140$ Hz. The data were zero-filled to 2048 points and processed using cosine-squared window function in both dimensions prior to Fourier transformation. The proton and carbon 90° pulse lengths were 6.9 and 12.5 ms, respectively. The $^1H—^{13}N$ HMBC experiments with PFG coherence selection using two PFG pulses were recorded with the following parameters: an acquisition time (at) 0.25 s, spectral windows of 6500 Hz (F2) and 24,000 Hz (F1); 2×256 increments in the ^{13}C dimension, 8 transients per increment and relaxation delay 1.5 s. This kind of experiment was optimized for $^nJ(C—H) = 8.0$ Hz. The proton and carbon 90° pulse lengths were 6.9 and 12.5 ms, respectively. The $^1H—^{15}N$ HMBC experiments with PFG coherence selection using two PFG pulses were recorded with the following parameters: an acquisition time (at) 0.25 s, spectral windows of 6500 Hz (F2) and 12,000 Hz (F1); 2×256 increments in the ^{15}N dimension, 16–32 transients per increment and relaxation delay 1.5 s, optimized for $^nJ(N—H) = 5.0$ Hz. The proton and nitrogen 90° pulse lengths were 7.2 and 30.0 ms, respectively.

EI mass spectra were run on an AMD M-40 instrument, electrospray ionization-mass spectra (ESI-MS) on a LCT (Micromass) apparatus. Flash chromatography was carried out using silica gel S 230–400 mesh (Merck) using hexane–ethyl acetate mixtures as an eluent. Calculations of electron charges on alkenyl carbon atoms and substrate HOMO/LUMO energies were calculated with the Hyperchem 7.5 program using semiempirical AM1 method.

2.2. Syntheses of dipolarophiles

Esters **3a,b** and **7** were prepared from the corresponding acids by esterification [19].

*2.2.1. Methyl cyclohex-1-ene-1-carboxylate (**3a**)*

It was obtained as a straw-colored oil, yield 60%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.99 (m, 1H, H3), 3.73 (s, 3H, H_3CO), 2.22 (m, 4H, H7, H4), 1.63 (m, 4H, H6, H5) ppm.

*2.2.2. L-Menthyl cyclohex-1-ene-1-carboxylate **(3b)***

N,N′-dicyclohexylcarbodiimide (DCC) (1.72 g, 8.34 mmol in dry CH_2Cl_2) was added with stirring at room temperature to a solution of cyclohex-1-ene-1-carboxylic acid (0.793 g, 6.3 mmol), L-menthol (1.04 g, 6.7 mmol) and 4-dimethyloaminopyridine (0.196 g, 1.6 mmol) in a mixture of dry dichloromethane/acetonitrile (5 mL, 1:1) under dry argon. Stirring was continued for 24 h. The reaction mixture was filtered and the filter paper was washed with dichloromethane. The solution was washed with water, dilute HCl, water, aqueous solution of sodium bicarbonate, and finally several times with water. The solution was dried ($MgSO_4$) and the product obtained after evaporation of the solvent was purified by flash chromatography on silica gel affording the expected menthyl ester **3b** as a yellowish wax (55%), mp. 29–30 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.95 (m, 1H, H3), 4.73 (td, J = 10.9; 4.3 Hz, 1H, H7′), 2.26 (m, 2H, H7), 2.18 (m, 2H, H4), 2.03 (dm, J = 12.0 Hz, 1H, H6′eq), 1.89 (septuplet d, J = 7.0; 2.7 Hz, 1H, H7′), 1.68 (m, 2H, H3′eq, H4′eq), 1.65 (m, 2H, H4′ax, H5), 1.60 (m, 2H, H4ax, H5ax), 1.51 (m, 1H, H5′), 1.42 (m, H2′), 1.08 (m, 1H, H3′ax), 0.98 (m, 1H, H6′ax), 0.90 (d, J = 6.6 Hz, 3H, H10′), 0.90 (d, J = 7.1 Hz, 3H, H8′), 0.87 (m, 1H, H4′ax), 0.77 (d, J = 6.9 Hz, H9′) ppm; ^{13}C (from HSQC, $CDCl_3$, 150 MHz): δ 139.0 (C3), 131.3 (C2), 74.2 (C8), 47.2 (C9), 40.9 (C13), 34.3 (C11), 31.4 (C12), 26.4 (C14), 25.7 (C4), 24.2 (C7), 23.5 (C3′), 22.2 (C6), 22.1 (C5), 21.5 (C10), 20.7 (C8), 16.7 (C9) ppm. HR ESI MS calcd. for $C_{17}H_{28}O_2Na$: 287.1987, found: 287.1974.

*2.2.3. Methyl cyclohex-3-ene-1-carboxylate (**7**)*

It was prepared [19] as a yellowish oil, yield 60%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.68 (m, 2H, H4, H5), 3.69 (s, 3H, H3CO), 2.57 (m, 1H, H2), 2.25 (m, 2H), 2.08 (m, 3H), 1.68 (m, 1H) ppm

*2.2.4. Methyl (2E)-3-(cyclohex-3-en-1-yl)prop-2-enoate **(12)***

(a) *(2E)-3-(cyclohex-3-en-1-yl)prop-2-enoic acid* **(11)** was obtained by the Knoevenagel condensation [20] of aldehyde **10** with malonic acid as a yellowish solid mp. 39–41 °C, yield 90%; IR (KBr): 3420, 3170, 3040, 2960, 2840, 2720, 2700, 2630, 2595, 2510, 2380, 1689, 1642, 1450, 1421, 1315, 1287, 1250, 1228, 1140, 1105, 1040, 980, 948, 915, 860, 750, 720, 695, 656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.30 (s, 1H, OH), 7.11 (dd, J = 15.7; 6.9 Hz, 1H, H3), 5.84 (dd, J = 15.7; 1.3 Hz, 1H, H2), 5.70 (m, 2H, H6, H7), 2.45 (m, 1H, H4), 2.10 (m, 3H), 1.98 (m, 1H), 1.85 (m, 1H), 1.48 (m, 1H) ppm; HR ESI MS calcd. for $C_9H_{11}O_2$: 151.0759, found: 151.0763.

(b) Ester **12** was obtained from the acid **11** as a yellow oil, yield 60%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.98 (dd, J = 15.8; 7.1 Hz, 1H, H3), 5.83 (dd, J = 15.8; 1.4 Hz, 1H, H2), 5.69 (m, 2H, H6, H7), 3.73 (s, 3H, H_3CO), 2.45 (m, 1H, H4), 2.16 (m, 1H, H9eq), 2.10 (m, 2H), 1.92 (m, 1H, H5ax), 1.83 (m, 1H, H9eq), 1.47 (m, 1H, H9ax) ppm; ^{13}C (from HSQC, $CDCl_3$, 150 MHz): δ 153.9 (C3), 127.5 (C6), 125.3 (C7), 118.8 (C2), 51.2 (H_3CO—C═O), 36.4 (C4), 30.1 (C9), 27.5 (C5), 24.4 (C8) ppm.

*2.2.5. Methyl (2E)-3-[(4S)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl]prop-2-enoate (**18**)*

(a) ***(2E)-3-[(4S)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl]prop-2-enoic acid*** **(17)** was obtained by the Knoevenagel condensation of aldehyde **16** with malonic acid [20] as a brown solid, yield 25%; IR (KBr): 3430, 3180, 3050, 2946, 2900, 2840, 2720, 2640, 2595, 2500, 2410, 2300, 1679, 1650, 1637, 1617, 1415, 1360, 1310, 1280, 1140, 1105, 1005, 985, 950, 890, 835, 800, 720, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.5 (s, 1H, OH), 7.39 (d, J = 15.6 Hz, 1H, H3), 6.25 (m, 1H, H5), 5.78 (d, J = 15.6 Hz, 1H, H2), 4.75 (d, J = 21.3 Hz, 2H, H_2C═C), 2.36 (m, 1H, H6eq), 2.32 (m, 1H, H8eq), 2.20 (m, 2H, H7, H8ax), 2.18 (m, 1H, H6ax), 1.93 (m, 1H, H9eq), 1.76 (s, 3H, H12), 1.53 (m, 1H, H9ax) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 173.3 (C═O), 149.8 (C3), 148.9 (C4), 139.5 (C5), 134.6 (C10), 114.3 (C2), 109.2 (C11), 40.6 (C7), 31.9 (C6), 26.9 (C9), 24.5 (C8), 20.8 (CH_3, C12); HR ESI MS calcd for $C_{12}H_{15}O_2$: 191.1072, found: 191.1069.

(b) Ester **18** was obtained from the acid **17** [19] as a yellowish oil, yield 65%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 15.8 Hz, 1H, H3), 6.19 (m, 1H, H5), 5.77 (d, J = 15.8 Hz, 1H, H2), 4.74 (dm, J = 16.5 Hz, 2H, H_2C═C), 3.75 (s, 3H), 2.34 (m, 1H, H6eq), 2.30 (m, 1H, H8eq), 2.17 (m, 3H, H7, H8ax, H6ax), 1.93 (m, 1H, H9eq), 1.75 (s, 3H, H12), 1.53 (m, 1H, H9ax) ppm.

*2.3. Cycloaddition reaction of dipolarophiles **3a, 3b, 7, 12, 18** with 4-trifluoromethylbenzonitrile oxide (**4**). A general procedure for preparation of **5**, **6**, **8**, **9**, **13**–**15**, **19**–**22***

4-Trifluoromethylbenzonitrile oxide (**4**) was generated as follows: a solution of the corresponding chloroxime (0.25 g, 1.12 mmol) in dry dichloromethane was passed through an Amberlyst-21 column and added dropwise over 30 min to the solution of a dipolarophile in dry dichloromethane, and the solution was stirred overnight at room temperature. Water was added, organic layer was separated and the aqueous one extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the product was purified by flash column chromatography.

*2.3.1. Methyl 3-[4-(trifluoromethyl)phenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazole-7a-carboxylate (aryl—CO_2Me cis) **(5a)***

It was obtained as a gray-green oil, yield: 20%; IR (KBr): 3447, 2960, 2850, 1740, 1625, 1440, 1410, 1325, 1275, 1280, 1250, 1175, 1129, 1105, 1068, 1015, 910, 845, 780, 675 cm^{-1}; ^{1}H, ^{13}C NMR see Tables 4 and 5; ESI-MS m/z 350 (M^++Na).

*2.3.2. Methyl 3-[4-(trifluoromethyl)phenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazole-7a-carboxylate (aryl—CO_2Me trans) **(6a)***

It was obtained as a white crystalline material, mp. 104–106 °C, yield 20%. ^{1}H, ^{13}C NMR see Tables 4 and 5; ^{15}N HMBC NMR ($CDCl_3$, 600 MHz): δ −11.1 (s, N2) ppm; ^{19}F NMR ($CDCl_3$, 470 MHz): δ −63.01 (s, CF_3) ppm; ESI MS m/z 350 (M^++Na); HR ESI MS calcd for $C_{16}H_{16}O_3NF_3Na$: 350.0980, found: 350.0984.

*2.3.3. L-Menthyl 3-(4-trifluoromethylophenyl)-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazole-7a-carboxylates **(5b, 6b)***

This were obtained as a grey wax, yield 25%; IR (KBr): 2928, 2860, 1725, 1620, 1456, 1410, 1360, 1324, 1280, 1247, 1169, 1131, 1069, 1050, 1015, 960, 880, 846, 770, 740, 600 cm^{-1}; ^{1}H, ^{13}C NMR see Tables 4 and 5; **5b** ^{15}N NMR (from ^{15}N—^{1}H HMBC, acetone, 600 MHz): δ −8.3 (s, N2) ppm. **6b** ^{15}N NMR (from ^{15}N—^{1}H

Table 1
Cycloaddition reactions of the dipole **4** to the dipolarofiles **3a**, **3b**.

No	Lewis acid	Ligand	Dipolarofile	Yield%	Products%			
					5a	**6a**	**5b**	**6b**
1	$Yb(OTf)_3$	A[a]	**3a**	20	0	100	–	–
2	$Yb(OTf)_3$	*R*-(+)-B[b]	**3a**	15	2	98	–	–
3	–	–	**3a**	35	48	52	–	–
4	$Yb(OTf)_3$	Rac-B	**3b**	18	–	–	55	45
5	$Yb(OTf)_3$	–	**3b**	25	–	–	58	42
6	–	–	**3b**	20	–	–	52	48

[a] A (+)-(4,6-benzylidene)methyl-α-D-glucopyranoside, Fig. 1.
[b] B 1,1′-bi-2-naphthol.

Table 2
Cycloaddition reactions of the dipole **4** to the dipolarofile **12**.

No.	Catalyst	Yield%	Products%					
			13a	**13b**	**14a**	**14b**	**15a**	**15b**
1	$Yb(OTf)_3$-A[a]	60	1	1	51.3	43.7	1.5	1.5
2	$Yb(OTf)_3$-C[b]	70	14	16	70	0	0	0
3	–	60	37	38	9.5	9.5	2.5	2.5

[a] (+)-(4,6-Benzylidene)methyl-α-D-glucopyranoside, Fig. 1.
[b] 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.

Table 3
Cycloaddition reactions of the dipole **4** to the dipolarofile **18**.

No.	Catalyst	Yield%	Products%				
			19a	**19b**	**20ab**	**21**	**22**
1	$Yb(OTf)_3$-A[a]	93	42	44	7	1	6
2	–	96	47	37	5	2	9

[a] (+)-(4,6-Benzylidene)methyl-α-D-glucopyranoside, Fig. 1.

HMBC, acetone, 600 MHz): δ −8.0 (s, N2) ppm; HR ESI MS calcd for $C_{25}H_{32}O_3NF_3Na$: 474.2232, found: 474.2216.

*2.3.4. Methyl 3-[4-(trifluoromethyl)phenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazole-6-carboxylate **(8)***

It was obtained as a green oil, yield 10%; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.00 (d, *J* = 8.3 Hz, 2H, H5′, H3′), 7.81 (d, *J* = 8.3 Hz, 2H, H6′, H2′), 4.65 (m, 1H, H5), 3.68 (s, 3H, H_3CO), 3.57 (m, 1H, H4), 2.57 (m, 1H, H7), 2.45 (m, H6eq), 2.19 (m, H9eq), 2.03 (m, H6ax), 1.95 (H8eq), 1.47 (m, H8ax), 1.25 (m, H9ax) ppm; ^{13}C NMR (from HSQC, acetone-d_6, 150 MHz) δ 131.1 (q, *J* = 32.8 Hz, C4′), 129.1 (C1′), 128.0 (C2′, C6′), 126.4 (q, *J* = 3.8 Hz, C3′, C5′), 124.5 (q, *J* = 272.0 Hz, CF_3), 81.4 (C5), 51.6 (OCH_3), 43.5 (C4), 38.0 (C7), 28.0 (C6), 26.3 (C9), 25.6 (C8) ppm.

*2.3.5. Methyl 3-[4-(trifluoromethyl)phenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazole-5-carboxylate **(9)***

It was obtained as a green oil, yield 10%; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.18 (d, *J* = 8.3 Hz, 2H, H5′, H3′), 7.93 (d, *J* = 8.3 Hz, 2H, H6′, H2′), 4.51 (m, 1H, H5), 3.61 (s, 3H, H_3CO), 3.65 (m, 1H, H4), 2.57 (m, 1H, H8), 2.31 (m, 1H, H9eq), 2.20 (m, 1H, H6eq), 2.00 (m, 1H, H7eq), 1.87 (m, 1H, H9ax), 1.60 (m, 1H, H6ax), 1.21 (m, 1H, H7ax) ppm; ^{13}C NMR (from HSQC, acetone-d_6, 150 MHz) δ 131.1 (q, *J* = 32.8 Hz, C4′), 129.1 (C1′), 128.0 (C2′, C6′), 126.4 (q, *J* = 3.8 Hz, C3′, C5′), 124.5 (q, *J* = 272.0 Hz, CF_3), 80.8 (C5), 51.5 (OCH_3), 43.7 (C4), 38.1 (C7), 28.0 (C6), 26.3 (C9), 25.0 (C8) ppm.

*2.3.6. Methyl 4-(cyclohex-3-en-1-yl)-3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazole-5-carboxylates (**13a, 13b**)*

This were obtained as a celadon oil; IR (KBr): 3030, 2960, 2920, 2850, 1762, 1740, 1640, 1618, 1438, 1412, 1328, 1320, 1280, 1240, 1209, 1160, 1121, 1067, 1014, 925, 880, 847, 775, 658, 640, 595 cm^{-1}; ^{1}H, ^{13}C NMR see Tables 6 and 7; EI MS *m*/*z* 353 (M^++H), 334 [(M^+−F)+H], 294 [(M^+—O═C—OCH_3) + H], 214 [(M^+-C_6H_9O═C—OCH_3) + H], 145 (F_3C—C_6H_4), 81 [(C_6H_9) + H], 80 (C_6H_9).

*2.3.7. Methyl 5-(cyclohex-3-en-1-yl)-3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazole-4-carboxylates (**14a, 14b**)*

This were obtained as a yellow oil, ^{1}H, ^{13}C NMR see Tables 6 and 7; (**14a**) ^{15}N NMR ($CDCl_3$, 600 MHz): δ −3.94 (s, N2) ppm; (**14b**) ^{15}N NMR ($CDCl_3$, 600 MHz): δ −3.95 (s, N2) ppm; ^{19}F NMR ($CDCl_3$, 471 MHz): δ −63.34 (s, F_3CAr) ppm; HR ESI MS calcd for $C_{18}H_{18}O_3NF_3Na$: 376.1136, found: 376.1148.

*2.3.8. Methyl (2E)-3-[3-(4-trifluoromethylphenyl)-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazol-6-yl]prop-2-enoate **(15a)** and methyl (2E)-3-[3-(4trifluoromethylphenyl)-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazol-5-yl]prop-2-enoate **(15b)***

This were obtained as a brown oil, yield 6%; **(15a)** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (m, 2H), 7.67 (m, 2H), 6.93 (dm, *J* = 16.0 Hz, 1H), 5.84 (dd, *J* = 16.0; 1.5 Hz, 1H), 4.62 (m, 1H), 3.75 (m, 3H), 2.47 (m, 1H), 2.17 (m, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.76 (m, 1H); **(15b)** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 6.85 (dd, *J* = 16.0; 7.0 Hz, 1H), 5.79 (dd, *J* = 16.0; 1.5 Hz, 1H), 4.54 (m, 1H), 3.71 (m, 3H), 2.47 (m, 1H), 2.17 (m, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.76 (m, 1H); HR ESI MS calcd. for $C_{18}H_{18}O_3NF_3Na$: 376.1136, found: 376.1126.

*2.3.9. Methyl (2E)-3-[(4S)-4-{5-methyl-3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazol-5-yl}cyclohex-1-en-1-yl)prop-2-enoates (**19a, 19b**)*

This were obtained as a yellowish wax, mp. 138–139 °C, yield 93%; IR (KBr): 3420, 2960, 2929, 2850, 1708, 1634, 1620, 1600, 1439, 1412, 1328, 1275, 1169, 1140, 1120, 1071, 1040, 975, 933, 842, 802, 780, 600 cm^{-1}; **19a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.73 (d, *J* = 8.2 Hz, 2H, H6′, H2′), 7.65 (d, *J* = 8.2 Hz, 2H, H5′, H3′), 7.30 (dd, *J* = 15.8; 3.4 Hz, 1H, H13), 6.17 (m, 1H, H9), 5.78 (d, *J* = 15.8 Hz, 1H, H14), 3.75 (s, 3H, H_3CO), 3.26 (d, *J* = 16.8 Hz, 1H,

Table 4
^{1}H NMR signals δ of **5a, 6a** (600 MHz, $CDCl_3$), and **5b, 6b** (acetone d_6) (*J* in Hz).

H	**5a**	**6a**	**5b**	**6b**
4	3.58 (dd, 12.7, 6.2)	3.88 (dd, 9.7, 7.3)	4.05 (dd, 10.9, 4.4)	3.97 (dd, 9.9, 7.1)
6eq, 6ax	2.10 (dm, 15.0), 1.79 (m)	2.34 (dt, 15.1, 3.6), 1.89 (ddd, 15.1, 12.5, 5.3)	2.23 (m), 1.94 (m)	2.28 (m), 1.98 (m)
7eq, 7ax	1.61 (dm, 12.7), 1.45 (dt, 13.5, 3.8)	1.72 (m), 1.55 (m)	1.73 (m), 1.48 (m)	1.73 (m), 1.48 (m)
8eq, 8ax	1.73 (dm, 13.9), 1.25 (m)	1.66 (m), 1.34 (m)	1.66 (m), 1.38 (m)	1.66 (m), 1.38 (m)
9eq, 9ax	1.25 (m), 1.13 (m)	2.10 (m), 1.26 (m)	2.23 (m), 1.22 (m)	2.28 (m), 1.22 (m)
2′	8.12 (d, 8.2)	7.81 (d, 8.2)	8.06 (d, 8.2)	8.02 (d, 8.2)
3′	7.74 (d, 8.2)	7.65 (d, 8.2)	7.82 (d, 8.2)	7.82 (d, 8.2)
5′	7.74 (d, 8.2)	7.65 (d, 8.2)	7.82 (d, 8.2)	7.82 (d, 8.2)
6′	8.12 (d, 8.2)	7.81 (d, 8.2)	8.06 (d, 8.2)	8.02 (d, 8.2)
OCH_3/1″	3.71 (s)	3.74 (s)	4.65 (td, 10.9, 4.4)	4.63 (td, 10.9, 4.4)
2″	–	–	1.42 (m)	1.42 (m)
3″	–	–	1.66 (m), 1.05 (m)	1.66 (m), 1.07 (m)
4″	–	–	1.66 (m), 0.89 (m)	1.66 (m), 0.89 (m),
5″	–	–	1.48 (m)	1.48 (m)
6″	–	–	1.86 (m), 1.02 (m)	1.91 (m), 0.99 (m)
7″	–	–	1.80 (m)	1.85 (m)
8″	–	–	0.63 (d, 7.1)	0.57 (d, 6.9)
9″	–	–	0.87 (d, 6.7)	0. 79 (d, 6.9)
10″	–	–	0.87 (m)	0.77 (d, 6.9)

Table 5
^{13}C NMR signals δ of **b** (50.3 MHz, $CDCl_3$), **6a** (125 MHz, $CDCl_3$), and **5b, 6b** (acetone d_6) (J ^{13}C-F in Hz).

C	5a	6a	5b	6b
3	159.0	162.2	163.3	163.0
4	51.9	46.3	46.8	47.3
5	87.6	88.0	88.8	88.9
6	30.8	27.6	28.2	28.0
7	20.1	19.5	20.6	20.5
8	23.4	20.7	21.7	21.6
9	26.6	26.0	26.9	27.0
O—C=O/10	173.5	174.1	172.8	173.4
1′	131.1	131.9	133.7	133.8
2′	128.2	127.4	128.4	128.4
3′	126.1 (q, 3.6)	125.8 (q, 3.4)	126.7 (q, 2.8)	126.7 (q, 2.8)
4′	132.0 (q, 27.5)	132.0 (q, 27.5)	132.0 (q, 26.9)	132.0 (q, 26.9)
5′	126.1 (q, 3.6)	125.8 (q, 3.4)	126.7 (q, 2.8)	126.7 (q, 2.8)
6′	128.2	127.4	128.4	128.4
1″/OCH_3	52.4	53.0	76.0	76.1
2″	–	–	47.8	47.8
3″	–	–	23.8	23.9
4″	–	–	34.9	34.9
5″	–	–	32.1	32.1
6″	–	–	41.3	41.2
7″	–	–	26.8	26.7
8″	–	–	16.2	16.2
9″	–	–	20.9	20.9
10″	–	–	22.2	22.3
CF_3	–	123.7 (q, 272)	125.1 (q, 271)	125.1 (q, 271)

Table 6
^{1}H NMR signals δ of **13a,b** ($CDCl_3$, 500 MHz) and **14a,b** (600 MHz) (J in Hz).

H	13a	13b	14a	14b
4	4.00 (dd, 4.0; 3.5)	4.05 (dd, 4.0; 3.5)	4.27 (d, 6.7)	4.27 (d, 6.7)
5	5.00 (d, 4.0)	5.02 (d, 4.0)	4.89 (dd, 6.7, 6.7)	4.86 (dd, 6.8, 6.7)
OCH_3	3.81 (s)	3.82 (s)	3.73 (s)	3.73 (s)
6	2.06 (m)	2.13 (m)	1.95 (m)	1.95 (m)
7eq, 7ax	2.16 (m), 1.99 (m)	2.13 (m), 1.99 (m)	2.14 (m), 1.86 (m)	2.21 (m), 1.95 (m)
8	5.66 (m)	5.66 (m)	5.69 (m)	5.69 (m)
9	5.63 (m)	5.63 (m)	5.69 (m)	5.69 (m)
10eq, 10ax	2.06 (m), 1.90 (m)	2.06 (m), 1.90 (m)	2.14 (m), 2.08 (m)	2.12 (m), 2.10 (m)
11eq, 11ax	1.82 (m), 1.72 (m)	1.82 (m), 1.49 (m)	1.79 (m), 1.44 (m)	1.95 (m), 1.44 (m)
2′	7.82 (d, 8.5)	7.82 (d, 8.5)	7.81 (d, 8.3)	7.81 (d, 8.3)
3′	7.68 (d, 8.5)	7.68 (d, 8.5)	7.66 (d, 8.3)	7.66 (d, 8.3)
5′	7.68 (d, 8.5)	7.68 (d, 8.5)	7.66 (d, 8.3)	7.66 (d, 8.3)
6′	7.82 (d, 8.5)	7.82 (d, 8.5)	7.81 (d, 8.3)	7.81 (d, 8.3)

Table 7
^{13}C NMR signals δ of **13a,b** (150.8 MHz, $CDCl_3$) and **14a, b** (125 MHz, $CDCl_3$) (J ^{13}C-F in Hz).

C	13a	13b	14a	14b
3 (C=N)	157.1	157.1	152.7	152.6
4	56.9	57.4	56.0	55.9
5	80.3	80.0	90.5	90.1
OCH_3	53.0	53.0	53.1	53.1
C=O	171.2	171.1	170.0	169.9
6	34.2	33.9	38.2	38.2
7	29.8	25.0	26.7	26.7
8	125.3	125.3	124.7	124.7
9	126.8	127.3	125.2	125.2
10	25.0	27.3	24.4	24.5
11	25.4	25.7	23.9	23.9
1′	127.5	127.5	127.5	127.5
2′	127.7	127.6	126.9	126.9
3′	125.9 (q, 3.9)	125.9 (q, 3.9)	125.7 (q, 4.1)	125.8 (q, 4.1)
5′	125.9 (q, 3.9)	125.9 (q, 3.9)	125.7 (q, 4.1)	125.8 (q, 4.1)
6′	127.7	127.6	126.9	126.9
4′	131.9 (q, 30.5)	131.9 (q, 30.5)	131.8 (q, 32.7)	131.8 (q, 32.7)
CF_3	123.7 (q, 259.9)	123.7 (q, 259.9)	123.7 (q, 271.2)	123.7 (q, 271.2)

H4a), 2.98 (d, J = 16.8 Hz, 1H, H4b), 2.43 (m, 1H, H8eq), 2.36 (m, 1H, H11eq), 2.18 (m, 1H, H11ax), 2.04 (m, 2H, H8ax, H12eq), 1.97 (m, 1H, H7), 1.47 (s, 3H, H6, H_3C), 1.44 (m, 1H, H12ax) ppm; ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 167.8 (C=O), 154.6 (C3), 147.1 (C13), 136.9 (C9), 134.9 (C10), 133.6 (C1′), 131.4 (q, J = 32.0 Hz, C4′), 126.6 (C6′, C2′), 125.6 (q, J = 3.8 Hz, C3′, C5′), 123.8 (q,

J = 272.0 Hz, CF_3), 115.2 (C14), 89.9 (C5), 51.5 (H_3CO), 43.0 (C4), 42.3 (C7), 27.8 (C8), 24.8 (C11), 23.8 (C6), 23.3 (C12) ppm; ^{19}F NMR ($CDCl_3$, 471 MHz): δ −63.23 (s, F_3C) ppm; ^{15}N NMR ($CDCl_3$, 600 MHz): δ −8.71 (s, N2) ppm; **19b**: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.73 (d, J = 8.2 Hz, 2H, H6′, H2′), 7.65 (d, J = 8.2 Hz, 2H, H5′, H3′), 7.30 (dd, J = 15.8; 3.4 Hz, 1H, H13), 6,17 (m, 1H, H9), 5.78 (d, J = 15.8 Hz, 1H, H14), 3.74 (s, 3H, H_3CO), 3.25 (d, J = 16.8 Hz, 1H, H4a), 3.00 (d, J = 16.8 Hz, 1H, H4b), 2.40 (m, 1H, H8eq), 2.36 (m, H11eq), 2.18 (m, H11ax), 2.08 (m, 1H, H8ax), 2.04 (m, H12eq), 1.96 (m, 1H, H7), 1.45 (s, 3H, H6, H_3C), 1.34 (m, 1H, H12ax) ppm; ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 167.8 (C═O), 154.7 (C3), 147.1 (C13), 136.8 (C9), 134.8 (C10), 133.4 (C1′), 131.4 (q, J = 32.0 Hz, C4′), 126.6 (C6′, C2′), 125.5 (q, J = 3.8 Hz, C3′, C5′), 123.8 (q, J = 272.0 Hz, Ar—CF_3), 115.0 (C14), 90.3 (C5), 51.4 (H_3CO), 42.5 (C4), 42.2 (C7), 27.6 (C8), 24.4 (C11), 23.4 (C6), 23.1 (C12) ppm; ^{15}N NMR ($CDCl_3$, 600 MHz): δ −8.72 (s, N2) ppm; HR ESI MS calcd for $C_{21}H_{22}O_3NF_3Na$: 416.1450, found: 416.1465.

2.3.10. Methyl 3-(4-trifluoromethylphenyl)-5-[4-(prop-1-en-2-yl)cyclohex-1-en-1-yl]-4,5-dihydro-1,2-oxazole-4-carboxylates (**20a,b**)

This were obtained as a celadon mush, yield 7%; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, J = 8.5 Hz, 2H, H2′, H6′), 7.66 (d, J = 8.5 Hz, 2H, H3′, H5′), 5.90 (m, 1H, H7), 5.36 (d, J = 6.5 Hz, 1H, H5), 4.73 (dm, J = 17.0 Hz, 2H, H13), 4.30 (d, J = 6.5 Hz, 1H, H4), 3.74 (s, 3H, H_3CO), 2.18 (m, 2H, H8eq, 11eq), 2.06 (m, 2H, H9ax, 11ax), 1.87 (m, 1H, H8ax), 1.73 (s, 3H, H_3C—C═C), 1.68 (m, 1H, H10eq), 1.54 (m,1H, H10ax) ppm; ESI MS m/z 393 (M^+).

2.3.11. Methyl 4-[(4S)-4-(3-{4-trifluoromethylphenyl}-5-methyl-4,5-dihydro-1,2-oxazol-5-yl)cyclohex-1-en-1-yl]-3-(4-trifluoromethylphenyl)-4,5-dihydro-1,2-oxazole-5-carboxylates (**21**)

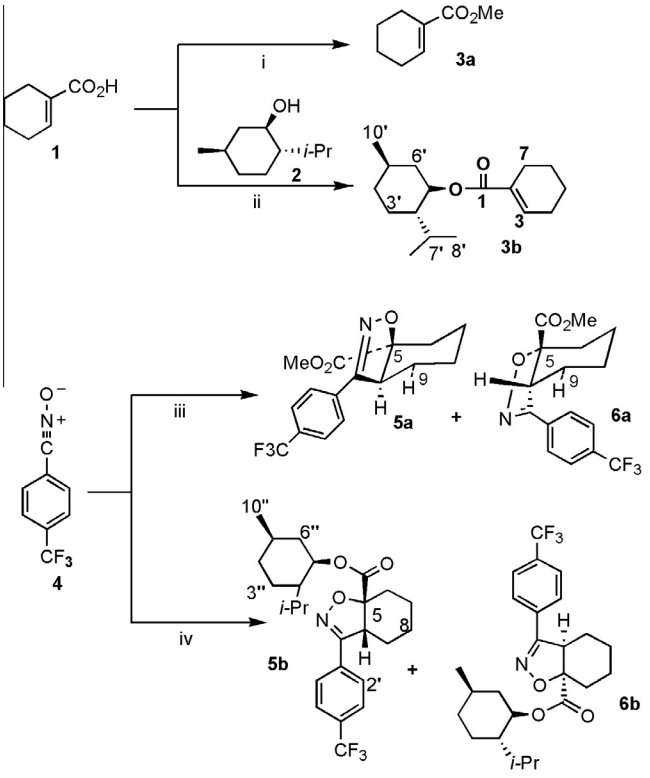
This were obtained as an oil, yield: 3%; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, J = 8.5 Hz, 2H, H2′, H6′), 7.81 (d, J = 8.0 Hz, 2H, H2″, H6″), 7.65 (d, J = 8.5 Hz, 2H, H3′, H5′), 7.65 (d, J = 8.0 Hz, 2H, H3″, H5″), 5.90 (m, 1H, H9), 5.36 (d, J = 6.3 Hz, 1H, H14), 4.28 (d, J = 6.3 Hz, 1H, H13), 3.74 (s, 3H, H_3CO), 3.23 (d, J = 16.8 Hz, 1H, H4a), 2.93 (d, J = 16.8 Hz, 1H, H4b), 2.30 (m, 2H), 2.17 (m, 2H), 1.74 (m, 2H), 1.57 (s, 3H, CH_3C), 1.38 (m, 1H) ppm; HR ESI MS calcd for $C_{29}H_{26}O_4N_2F_6Na$: 603.1694, found: 603.1696.

2.3.12. Methyl (2E)-3-[(4S)-4-(2-methoxypropan-2-yl)cyclohex-1-en-1-yl]prop-2-enoate (**22**)

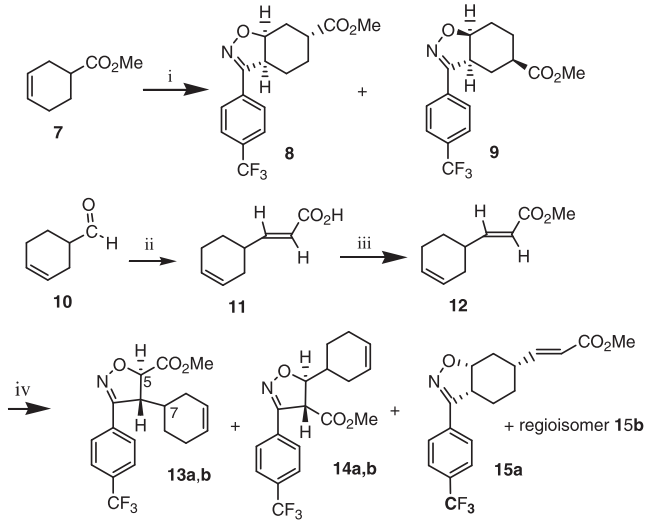
It was obtained as a celadon oil, yield: 12%; IR (neat): 2970, 2947, 2830, 1719, 1632, 1623, 1615, 1460, 1434, 1380, 1364, 1308, 1285, 1270, 1167, 1079, 1050, 1020, 982, 925, 860, 823, 802, 740, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, J = 15.8 Hz, 1H, H3), 6.18 (m, 1H, H5), 5.77 (d, J = 15.8 Hz, 1H, H2), 3.74 (s, 3H, H_3CO—C═O), 3.19 (s, 3H, H_3COC), 2.31 (dm, J = 13.2 Hz, 1H, H9eq), 2.26 (dt, J = 13.5; 5.0 Hz, 1H, H6eq), 2.12 (m, 1H, H9ax), 2.04 (m, 1H, H6ax), 1.95 (m, 1H, H8eq), 1.73 (m, 1H, H7), 1.26 (m, 1H, H8ax), 1.14 (s, 3H, H11, H_3CC), 1.12 (s, 3H, H12, H_3CC) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.3 (C═O), 147.9 (C3), 138.9 (C5), 135.1 (C4), 114.8 (C2), 76.5 (C10), 51.7 (H_3-CO—C═O), 49.1 (H_3COC), 42.1 (C7), 28.3 (C6), 25.4 (C9), 23.4 (C8), 22.3 (C11, H_3CC), 22.2 (C12, H_3CC) ppm. ESI MS m/z 261 (M^++Na); EI MS m/z 239 (M^++H), 206 [M^+—(H_3CO)—H], 73 [(H_3C)$_2$—$COCH_3$].

2.4. Fungicidal testing

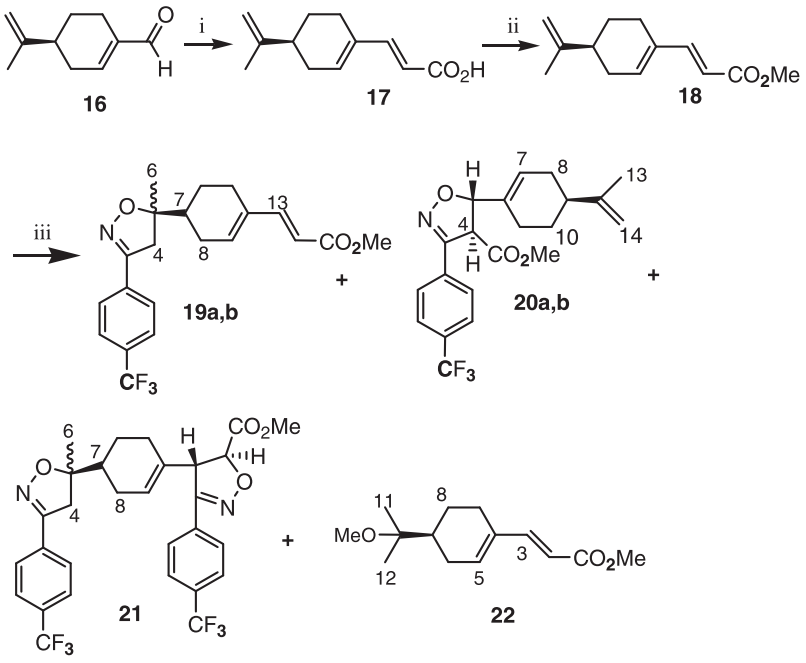
The compounds were screened for fungicidal activity *in vitro*. The tests were carried out for *Fusarium culmorum* (*F. c.*), *Phytophthora cactorum* (*P. c.*), *Rhizoctonia solani* (*R. s.*), and *Botrytis cinerea* (*B. c.*), and involved determination of mycelial growth retardation in potato glucose agar (PGA). Stock solutions of test chemicals in acetone were added to agar medium to give a concentration of 200 mg/L and dispersed into Petri dishes. Four discs containing the test fungus were placed at intervals on the surface of the solidified agar and the dishes were then inoculated for 4–8 days depending on the growth rate of the control samples, after which fungal growth was compared with that in untreated control samples. The fungicidal activity was expressed as the percentage of fungi linear growth inhibition compared to that of the control.



Scheme 1. Cycloaddition of dipole **4** to dipolarophiles **3a,b**. i MeOH, H^+, ii DCC, DMAP, iii **3a**, CH_2Cl_2, $Yb(OTf)_3$-ligand A (Fig. 1) or $Yb(OTf)_3$-ligand B or without the catalyst, iv **3b**, CH_2Cl_2, $Yb(OTf)_3$-rac ligand B or without the catalyst.



Scheme 2. Cycloaddition of the dipole **4** to the dipolarophiles **12**. i **4**, CH_2Cl_2, ii $CH_2(CO_2H)_2$, Py, morpholine, iii MeOH, H^+, iv **4**, CH_2Cl_2, $Yb(OTf)_3$-ligand A (Fig. 1) or $Yb(OTf)_3$-ligand C or without the catalyst.



Scheme 3. Cycloaddition of the dipole **4** to the dipolarophile **18**. i $CH_2(CO_2H)_2$, Py, morpholine, ii MeOH, H^+, and iii **4**, CH_2Cl_2, $Yb(OTf)_3$-ligand A or without the catalyst.

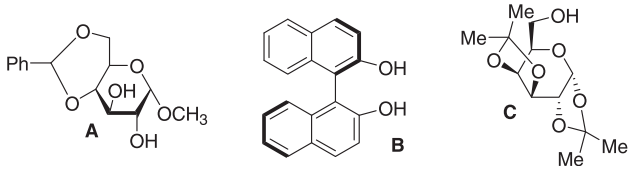


Fig. 1. Chiral ligands used in nitrile oxide cycloaddition reactions.

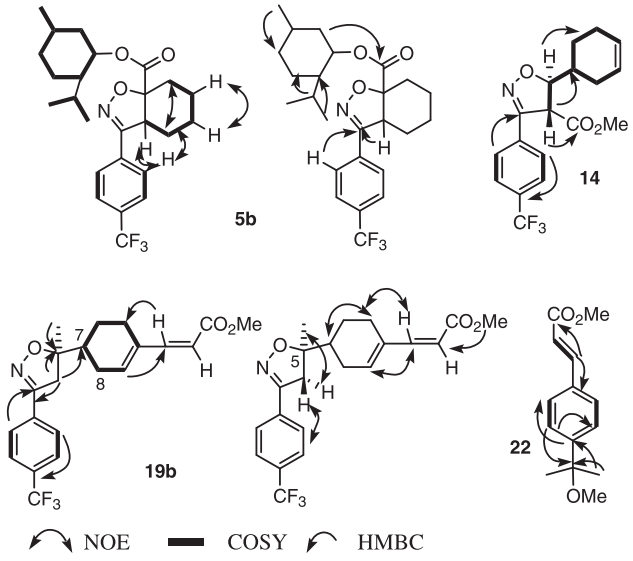


Fig. 2. Selected COSYs, NOEs and HMBC for adducts **5b**, **14**, **19b** and **22**.

3. Results and discussion

3.1. Structural analysis of the cycloadducts

We have examined [2+3] cycloaddition of 4-(trifluoromethyl)benzonitrile oxide (**4**) to cyclohexene carboxylates **3a**, **3b**, **7**, and to cyclohexenes functionalized with alkenoate and alkenyl substituents **12** and **18**. The compounds described in this work are presented in Schemes 1–3 and Figs. 1–3. Cycloaddition product and catalysts applied are displayed in Tables 1–3. ^{1}H NMR chemical shifts and multiplicities of adducts **5a,b; 6a,b** and **13a,b**; **14a,b** are shown, respectively, in Tables 4 and 6. ^{13}C NMR chemical shifts of adducts **5a,b; 6a,b** and **13a,b; 14a,b** are shown, respectively, in Tables 5 and 7. The spectroscopic data for the other products were presented in the experimental section.

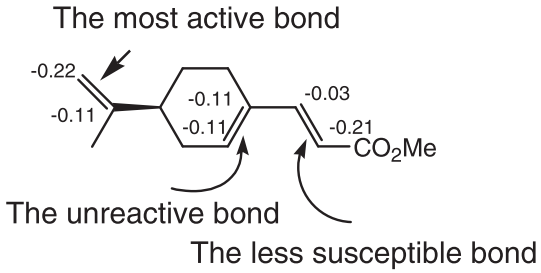


Fig. 3. Partial electron charges on atoms of interest involved in reaction of **18** and **4**.

Cycloaddition of 4-trifluoromethylbenzonitrile oxide (**4**) to ester **3a** without a catalyst afforded a mixture in 1:1.1 ratio of diastereoisomers **5a** and **6a** separated by column chromatography as the only regioisomers (Table 1). Diastereoselectivity of the reaction was dramatically improved after application of catalysts. The chiral ligands used in these studies are displayed in Fig. 1. Use of complexes of ytterbium triflate-(+)-(4,6-benzylidene)methyl-α-D-glucopyranoside (A) and ytterbium triflate-*R*-BINOL (B) furnished ester **6a** as the only product in the first case, and a 98:2 mixture of **6a, 5a**. We have applied before these and other catalytic systems to mediate the cycloaddition reaction of aryl nitrile oxides and crotonamides and cinnamides [11]. No hydrogen atom was observed on C5 in both isomers **5a, 6a** which would occur in the other regioisomers as proved by the HSQC spectra. This result can be rationalized by steric factors and dominant orbital control.

Reactions of the alkenes with electron-donating substituents and moderately electron-withdrawing substituents (as an ester group) are controlled by $LUMO_{dipol}$–$HOMO_{alkene}$ (ΔE = 8.67 eV)

interaction since $LUMO_{alkene}$–$HOMO_{dipol}$ energy gap (ΔE = 9.98) is higher [21]. Bond formation between atoms of the larger orbital coefficients leads to the 5-substituted fused isoxazolines [22].

Mass spectrometry showed molecular weight of 327 m.u. for both isomers and HR ESI MS confirmed the composition $C_{16}H_{16}F_3NO_3Na$. Configuration of **5a** with a cis relationship of the carbonylmethoxy and aryl group, and **6a** with a trans relationship of these groups was established from analysis of the NMR spectra. In ^1H NMR of **6a** the diagnostic proton 9eq showed a large chemical shift at 2.10 ppm and in isomer **5a** this proton absorbed at 1.25 ppm. This difference can be explained by the deshielding effect of the proximal aromatic ring in **6a** isomer.

Cycloaddition of the L-menthyl ester **3b** afforded cis-fused diastereoisomers **5b, 6b** in 1.4:1 ratio. In both isomers close position of H4 and aromatic protons H2′, H6′ was found. Structure **5b** was assigned to the major isomer based on position at the lower field of H4 proton slightly more deshielded by the carbonyl group than the respective proton of **6b**, as indicated by molecular modelling.

Cycloaddition of the unconjugated ester **7** afforded unseparable mixture of cis-fused regioisomers **8** and **9** in 7:3 ratio in a low 20% yield. On the other hand reaction of the conjugated, activated ester **3a** gave in the same conditions cycloadducts **5a, 6a** in 35% yield (Table 1). The structure **8** was ascribed to the major isomer because of position at the lower field of the diagnostic H5 proton at 4.65 ppm (deshielded by β-methoxycarbonyl group) than H5 in the other regioisomer **9** (4.51 ppm). This direction of addition was favored by the orbital factors. The reaction is LUMO-dipole controlled and oxygen atom of the dipole tends to attack the dipolarophile atom closer to the substitution position.

Cycloaddition to the dipolarophile **12** without any catalyst afforded a mixture of regioisomeric major adducts to the exocyclic double bond **13a,b** (75%) and **14a,b** (19%) as well as a mixture of minor adducts to the cyclohexene ring, **15a,b** (5%) in an overall 60% yield (Table 2). An application of the catalyst (ytterbium triflate and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) (Fig. 1, ligand C) reversed the regioselectivity and favored formation of isomer **14a** (70%); isomers **13a** (14%) and **13b** (16%) were also present. The other catalyst (ytterbium triflate-(+)-(4,6-benzylidene)methyl-α-D-glucopyranoside, ligand A) showed very good stereochemistry. The main products were regioisomers **14a,b** (95%); the minor isomers **13a,b** and **15a,b** were formed with, respectively, only 2% and 3% yields.

A complete assignment of ^1H and ^{13}C NMR spectra of **13a,b** and **14a,b** adducts based on analysis of 1D and 2D ^1H and ^{13}C NMR spectra (COSY, HSQC and HMBC) is presented in Tables 6 and 7. In both pairs trans relationship of H5—H4 protons reflects *E* configuration of the dipolarophile **12** preserved in the cycloaddition reaction. Regiochemistry shown for **13a,b**/**14a,b** was proven by observation of a strong correlation in the HMBC spectrum of **14a,b** between H5 and C7 and ^1H NMR spectrum. In diastereoisomeric pair **14a,b** (47:53 mixture) the diagnostic proton H5 was a doublet of doublets at, respectively, 4.89 and 4.86 ppm coupled to the adjacent H4 and H6 protons. In diastereoisomeric pair **13a,b** the diagnostic proton H5 was a doublet at respectively, 5.00 and 5.02 ppm coupled only to the H4 proton. An analysis of the COSY spectrum enabled also assignment of all signals of the cyclohexene moiety. Configuration of **14b** was ascribed to the more populated isomer because of the position of H7eq proton at a slightly lower field in result of deshielding effect of the adjacent ester group.

Reaction of the nitrile oxide **4** with the dipolarophile **18** afforded mainly diastereoisomeric adducts to the exocyclic propenyl group **19a,b** in 80% yield (Table 3). The minor products were formed by cycloaddition to the conjugated exocyclic double bond – **20a,b** (5%), reaction mixture contained also products **21** of a double cycloaddition, and an unexpected side product **22**. Reaction mediated by ytterbium triflate-(+)-(4,6-benzylidene)methyl-α-D-glucopyranoside was highly regio- and site-selective and afforded only **19a,b** pair. Formation of the major products **19a,b,** epimers at C5, by cycloaddition to the propenyl side chain was proved by presence of the geminally coupled H4 protons of isoxazoline as doublets at 3.25, 3.26 and 2.98, 3.00 ppm with a large coupling constant of 16.8 Hz. There was no hydrogen atoms at C5 (90.1 ppm) expected in the other regioisomer as shown by 2D HSQC NMR spectrum. An unsaturated conjugated ester moiety was preserved as witnessed by presence of the *E*-olefin (doublets at 7.30 and 5.78 ppm with coupling constant of 15.8 Hz in ^1H NMR spectrum as well as signals at 147.1 and 115.2 ppm in ^{13}C NMR spectrum, and cyclohexene double bond (multiplet at 6.17 ppm of H9 and peaks at 136.9 and 134.9 pm in ^{13}C NMR spectrum). Correlation in the 2D NMR NOESY spectrum in **19b** epimer between H4b and C5—CH_3 protons and a correlation in **19a** isomer between H4a and H7 proton at 1.96 ppm allowed to establish the structure of two diastereoisomers. High resolution electrospray mass spectrometry exhibited the quasi-molecular formula as $C_{21}H_{22}O_3NF_3Na$ for the products.

The minor diastereoisomeric products **20a,b** differing in relative orientation of H5 and propenyl substituent were formed in ca 7% yield by cycloaddition to the conjugated exocyclic double bond. ^1H NMR spectrum showed vicinally coupled H4 and H5 protons of 2-isoxazoline moiety as doublets at, respectively, 5.37 and 4.30 ppm with a coupling constant of 6.8 Hz, and a cyclohexene fragment with an exocyclic propenyl group. Structures with position of the ester function at C4 of isoxazoline ring was proposed based on the observed larger values of H4,5 coupling constant ($J > 4$ Hz) and the larger difference of chemical shifts in 4-esters and amides ($\Delta\delta > 1$ ppm) than in 5-esters and amides, where respective values were $J > 4$ Hz and ($\Delta\delta < 1$ ppm [11].

The second minor products were bis-adducts **21** (a mixture of four unseparable diastereoisomers) showing similar regioselectivity of the dipole addition to both exocyclic double bonds as found in the compounds **19a,b** and **20**. High resolution electrospray mass spectrometry exhibited the quasi-molecular formula as $C_{29}H_{26}O_4N_2F_6Na$ for the products.

A quite unexpected product was a methoxy ester **22**. ^1H NMR spectrum displayed a methyl cyclohexene acrylate fragment as in the dipolarophile, two aliphatic singlet methyl groups at 1.12 and 1.14 ppm, and an extra methoxy group at 3.19 ppm. ^{13}C NMR spectrum contained only four olefinic carbon atoms at 147.9, 138.9, 135.1, and 114.8 ppm. EI MS showed the molecular weight of 238 m.u. and fragmention ions at *m*/*z* at 206 corresponding to a loss of methanol, and the parent ion at *m*/*z* 73 corresponding to Me_2COMe composition. These results indicated that an addition of methanol to the very reactive exocyclic propenyl double group took place. This conclusion was confirmed by the presence of a new quaternary carbon atom at 76.5 ppm showing in HMBC spectrum correlations with OCH_3 group protons at 3.19, H8, and CH_3—C10 protons. The only source of the methoxy group could be the ester function.

Table 8 gives the positions of the nitrogen N-2 atom in isoxazoline-2 derivatives. The found values lie in the range characteristic for isoxazolines-2 described in the literature [23]. The most negative values of δ −11.1 ppm occurred for systems with just one hydrogen in the isoxazoline-2 ring at C4 in adduct **6a**. Less negative

Table 8
^{15}N NMR signals δ [a] (600 MHz, $CDCl_3$) of **6**, **14**, **19**.

N	6a	14a	14b	19a	19b
2	−11.1	−3.93	−3.95	−8.71	−8.72

[a] Obtained from 2D 15N—^1H HMBC correlations.

Table 9
Electron charges at the alkenyl carbon atoms of the dipolarophiles **3a,b**, **12**, **18,** and regioselectivity in the cycloaddition reaction.

Dipolarophile/C atom	C2	C3	C10	C11	C4/C6	C5/C7	Site selectivity	Regioselectivity	
								Reg. 4	Reg. 5
3a	−0.14	−0.08	–	–	–	–	C2/C3	1	1.1
3b	−0.14	−0.08	–	–	–	–	C2/C3	1[a]	1.4[b]
12	−0.20	−0.06	–	–	−0.17	−0.16	C2/C3	1	4
18	−0.21	−0.03	−0.11	−0.22	−0.11	−0.11	C10/C11	0	100

[a] Regioisomer **5b**.
[b] Regioisomer **6b**.

values are found for a system where there are two hydrogens on one carbon atom, as in compounds **19a,b**. The least negative values $\delta = -3.93$ ppm, and $\delta = -3.95$ ppm were observed in the compounds with hydrogens at the adjacent carbon atoms C4 and C5 in compounds **14a** and **14b**.

3.2. Rationalization of the observed site selectivity and regioselectivity

Table 9 gives electron charges at the alkenyl carbon atoms of the dipolarophiles **3a,b**, **12**, **18**, and the observed regioselectivity in the cycloaddition reaction.

For compound **18** a linear dependence of the reactivity on electron charges at the alkenyl carbon atoms can be observed (Fig. 3). The greater was the amount of negative charges of both carbon atoms of the double bond, the higher was the reactivity of the cycloaddition reaction. The most negative C10—C11 bond is the most reactive. The total charges at C10—C11 of −0.33 correspond to the formation of 96% of the products **19a,b**. The C2—C3 bond with total −0.24 is less reactive because it gave rise to only 6% of the product **20a,b**. The C4—C-5 bond (charges of −0.22) showed no reactivity in the reaction of cycloaddition. With diminishing bond electron charges decreased regioselectivity of the reaction from triene **18** to mono alkenes **3a,b**. An exception was compound **12** where the cyclohexenyl bond showed lower reactivity than the exocyclic one in spite of higher electron density. It could be rationalized by the steric effects and a more difficult approach of the dipole to the hindered internal double bond of the dipolarophile.

3.3. Biological activity of the products

A pair of diastereoisomers **14a, 14b** showed a much higher activity then the other regioisomeric pair **13a**, **13b**. A nearly pure **13a** is more active than the sum (**13a** + **13b**), which implies that the diastereoisomer **13b** is less active. Diastereoisomer **5a** shows some activity while the diastereoisomer **6a** of somewhat different spatial structure showed no potency. One can see very clearly the impact of the spatial structure on the fungicidal activity. This supports the value of testing pure isomers (see Table 10).

The dipolarofiles have also been screened, as well as the side product **22**. Particularly active was the acid **11** which showed fungicide activity comparable with that of the commercial fungicide chlorothalonil.

Table 10
Fungicidal inhibitory activities[a] of compounds **5, 6, 11, 12, 13, 14, 18, 22** at 200 mg/L.

Compound	*B. c.*[b]	*F. c.*	*P. c.*	*Rh. s.*
5a	38.0	16.0	0.0	0.0
6a	0.0	0.0	0.0	0.0
5b + **6b**	0.0	0.0	0.0	0.0
11	50.0	18.0	100	100
12	34.0	14.0	10.3	36.0
13a	42.0	4.0	2.6	38.0
13a + **13b**	28.9	0.0	0.0	0.0
14a + **14b**	74.0	44.0	41.0	64.0
18	26.7	38.0	60.0	64.0
22	73.4	44.0	2.4	46.7
Chlorothalonil[c]	80	38	61	88

[a] Percentage of linear growth inhibition.
[b] *B. c.* – *Botrytis cinerea*, *F. c.* – *Fusarium culmorum*, *P. c.* – *Phytophtora cactorum*, *Rh. s.* – *Rhizoctonia solani*.
[c] Reference compound.

4. Conclusions

High regio- and site selectivity of 1,3-dipolar cycloaddition reaction of 4-trifluoromethylbenzonitrile oxide to trienic ester **18** was observed. A correlation of double bond reactivity with electron charges was found. The addition to the exocyclic propene group was strongly favored. Cycloaddition to the ester **12** occurred with a good site selectivity to the conjugated double bond. Both selectivities were influenced by application of the catalysts. With ytterbium triflate-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose the regioselectivity was reversed to 30:70 and site selectivity improved – no addition to the isolated double bond was found. With the other catalyst (ytterbium triflate-(+)-(4,6-benzylidene)methyl-α-D-glucopyranoside) this trend was magnified and mainly regioisomer-4 was formed (95:2) with site selectivity strongly biased towards conjugate addition (97:3). Use of ytterbium triflate-(+)-(4,6-benzylidene)methyl-α-D-glucopyranoside complex resulted in 100% regio- and diastereoselectivity and furnished ester **6a** as the only product. These data demonstrate a high importance of the catalyzed cycloadddition reactions.

All diastereoisomeric products were fully characterized by ^{1}H and ^{13}C NMR 1D and 2D spectroscopy. Some dipolarophiles and adducts showed good fungistatic activity. Further research is in progress to analyze the biological potency of the new products, to improve regioselectivity of the cycloaddition reaction and to explain formation of the side-product.

Acknowledgement

This work was supported in part by the Polish Ministry of Science and Higher Education Research (Grant No. N209 003 638), which is gratefully acknowledged.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2013.12.035.

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