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Article

NMR Studies on 1,3-Dipolar Cycloaddition of Nitrile Oxides to Norbornenes

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A reação de cicloadição 1,3-dipolar de óxidos de nitrila a norbornanos substituídos com um grupo derivado de acrilato foi examinada. Somente adutos para o sistema norbornano foram formados com boa *exo* seletividade e completa seletividade ao sítio. As estruturas dos produtos foram elucidadas através das técnicas de espectrometria de massas com ionização por *electrospray* (ESI-MS) e de ressonância magnética nuclear (RMN) 2D de ^{1}H e ^{13}C.

The 1,3-dipolar cycloaddition reaction of nitrile oxides to norbornenes substituted with an acrylate-derived moiety was examined. Only adducts to norbornene system were formed with a good *exo* selectivity and complete site-selectivity. Structures of the products were elucidated by an extensive application of electrospray ionization-mass spectrometry (ESI-MS) and 2D ^{1}H and ^{13}C nuclear magnetic resonance (NMR).

Keywords: 1,3-dipolar cycloaddition, norbornenes, nitrile oxides, 2D NMR

Introduction

The 1,3-dipolar 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] Reactions of monosubstituted and 1,1-disubstituted alkenes furnish regioselectively 5-substituted 2-isoxazolines while 1,2-disubstituted olefins usually afford mixtures of regio- and stereoisomers.

The nitrile oxides can be formed either by the 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]

The 1,3-dipolar cycloaddition of nitrile oxides to bicyclic alkenes was examined before. For example, norbornadienes afforded mixtures of *exo*- and *endo*-adducts in ca. 4:1 ratio in reaction with benzonitrile oxide and alpha-oxophenylacetonitrile oxide. Reaction of nitrile oxides with norbornadienes substituted with electron deficient groups in 2,3-positions afforded only adducts to the more electron-rich unsubstituted double bond.[5] On the other hand, 1,3-dipolar cycloaddition to norbornenes follows the *exo* rule without exception for symmetrically as well as for unsymmetrically substituted bicyclic systems, although generally mixtures of regioisomers were observed.[6]

Another problem is site-selectivity of nitrile oxide cycloaddition to polyunsaturated alkenes. In cycloaddition of benzonitrile oxide to 2-alkoxy-1,3-butadienes, only the unsubstituted vinyl group participated in the reactions, while in case of alpha-oxophenylacetonitrile oxide, both double bonds reacted.[7] This result indicated the dominance of steric effects over electronic ones in the first case, in which more sterically demanding dipole did not interact with the activated, electron richer disubstituted 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 affording exclusively *exo* cycloadducts.[8]

Some norbornane derivatives show biological activity. 3-Methylene-2-norbornanone was identified as a potent anti-proliferative agent.[9] Racemic *gluco*-configured norbornanes are inhibitors of β-glycosidases.[10]

Our group has been interested in studies on activity of 2-isoxazolinecarboxamides as plant protecting agents.[11] Therefore, it was envisaged that fusion of the norbornene system with the isoxazoline carboxamide moiety would be a promising approach to new biologically active products. Herein, the results of our work on 1,3-dipolar cycloaddition of 4-(trifluoromethyl)benzonitrile oxide to norbornenes substituted with alkenoyl groups are presented. Analysis

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of the reaction products was quite a challenge. There were two reactive double bonds in the dipolarophiles, all three dipolarophiles were mixtures of epimers, and two regioisomers were expected for each of the epimers. The problems were even more complex for dipolarophile **4**, in which a chiral menthyl ester function was introduced to study effects of a remote group on regioselectivity and site-selectivity of the reaction. These structural problems were solved using 1D and 2D nuclear magnetic resonance (NMR) spectroscopy.

Experimental

Materials and spectral measurements

Reagent-grade chemicals were used without further purification unless otherwise noted. Spectra were recorded as follows: IR spectra on a JASCO FTIR-420 spectrometer, ^{1}H, ^{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. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard, coupling constants are reported in Hz. 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. Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and *N*-chlorosuccinimide (NCS) in *N*-dimethylformamide (DMF).[12]

Syntheses of dipolarophiles **3-5**

Methyl *E*-3-bicyclo[2.2.1]hept-5-en-2-ylprop-2-enoate (**3a,b**) was prepared as a mixture 3/1 of *endo* and *exo* isomers from the commercial bicyclo[2.2.1]-hept-5-ene-2-carboxaldehyde (**1**) (mixture of epimers) in the Knoevenagel condensation with malonic acid via acid **2** followed by acidic esterification.[13] Structures of both isomers were elucidated by analyses of ^{1}H, ^{13}C and HSQC spectra (Scheme 1, Tables 1 and 2). HRESIMS calcd. for $C_{11}H_{14}O_2Na$: 201.0892, found: 201.0900.

Exo-methyl 3-bicyclo[2.2.1]hept-5-en-2-yl-prop-2-enoate (**3b**) was obtained by linear co-dimerization

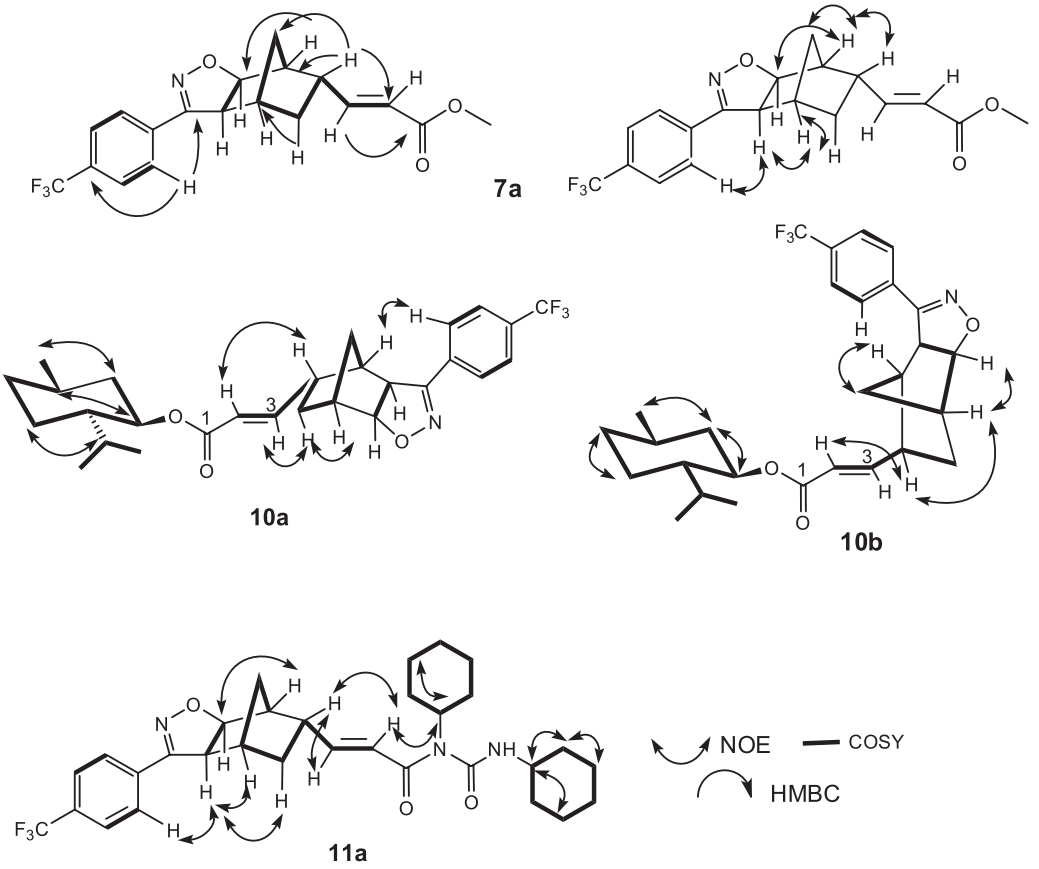


Figure 1. Selected NOE, COSY and HMBC correlations for adducts **7a**, **10a**, **10b** and **11a**.

Table 1. ^{1}H NMR signals δ of the dipolarophiles **3a,b**, **5a,b** ($CDCl_3$), and **4a,b** $(CD_3)_2CO$ (*J* in Hz)

H	3a	3b	4a	4b	5a	5b
2	5.79 (dd,15.6, 0.9)	5.84 (dd, 15.6, 1.0)	5.78 (dd, 15.6, 3.3)	5.84 (dd, 15.5, 1.0)	6.08 (d, 14.7)	6.12 (dd, 15.0, 1.0)
3	6.62 (dd, 15.6, 9.0)	6.99 (dd, 15.6, 8.9)	6.55 (dd, 15.6, 7.4)	6.94 (dd, 15.5, 8.9)	6.57 (dd, 14.7, 9.0)	6.92 (dd, 15.0, 9.0)
4	2.85 (m)	2.18 (m)	2.92 (m)	2.20 (m)	2.86 (m)	2.17 (m)
5	2.91 (m)	2.93 (m)	2.88 (m)	2.92 (m)	2.90 (m)	2.93 (m)
6	6.22 (dd, 5.7, 3.1)	6.13 (m)	6.24 (m)	6.14 (m)	6.20 (dd, 5.4, 3.0)	6.12 (m)
7	5.98 (dd, 5.7, 2.8)	6.13 (m)	5.97 (m)	6.14 (m)	5.98 (dd,5.4, 2.7)	6.12 (m)
8	2.91 (m)	2.72 (m)	2.88 (m)	2.70 (m)	2.90 (m)	2.70 (m)
9	1.98, 0.91 (m)	1.42, 1.38 (m)	1.90, 1.49 (m)	1.70, 1.38 (m)	1.97, 0.90 (m)	1.44, 0.90 (m)
10	1.47, 1.31 (m)	1.44, 1.42 (m)	1.42. 1.32 (m)	1.42, 1.38 (m)	1.46, 1.31 (m)	1.44, 1.38 (m)
1’	3.71 (s)	3.74 (s)	4.69 (m)	4.72 (m)	3.97 (m)	4.01 (m)
2’	–	–	1.42 (m)	1.42 (m)	1.81, 1.31 (m)	1.81, 1.31 (m)
3’	–	–	1.70, 1.11 (m)	1.70, 1.11 (m)	1.63, 1.16 (m)	1.63, 1.16 (m)
4’	–	–	1.70, 0.90 (m)	1.70, 0.90 (m)	1.91, 1.81 (m)	1.91, 1.81 (m)
5’	–	–	1.54 (m)	1.54 (m)	1.63, 1.16 (m)	1.63, 1.16 (m)
6’	–	–	2.00, 1.04 (m)	2.00, 1.04 (m)	1.81, 1.31 (m)	1.81, 1.31 (m)
7’/1”	–	–	1.93 (m)	1.93 (m)	3.71 (m)	3.70 (m)
8’/2”,6”	–	–	0.90 (d,)	0.90 (d,)	1.94, 1.26 (m)	1.97, 1.26 (m)
9’/3”,5”	–	–	0.75 (d, 6.9)	0.77 (d, 6.9)	1.72, 1.38 (m)	1.72, 1.38 (m)
10’/4”	–	–	0.90 (d,)	0.90 (d,)	1.63, 1.26 (m)	1.63, 1.26 (m)

Table 2. ^{13}C NMR signals δ of the dipolarophiles **3a,b**, **5a,b** ($CDCl_3$), **4a,b** $(CD_3)_2CO$

C	3a	3b	4a	4b	5a	5b
1	166.5	166.0	166.1	166.2	167.2	166.9
2	119.9	119.6	121.5	121.2	121.5	121.2
3	154.1	154.1	154.2	154.0	152.7	152.6
4	41.9	41.5	42.4	42.3	42.2	41.8
5	47.8	42.3	48.5	48.5	48.0	42.3
6	138.0	137.9	138.5	138.1	137.8	137.6
7	132.4	137.9	133.1	133.0	132.1	135.9
8	42.8	47.8	43.5	43.0	42.9	47.9
9	32.4	32.5	33.1	33.0	32.9	32.2
10	49.6	45.5	50.2	46.0	49.7	45.6
1’	51.4	51.4	73.8	73.8	56.3	56.1
2’	–	–	47.9	46.0	26.3	26.3
3’	–	–	24.1	24.3	25.4	25.4
4’	–	–	35.0	34.2	30.8	30.8
5’	–	–	32.1	32.0	25.4	25.4
6’	–	–	41.8	41.7	26.3	26.3
7’/1”	–	–	27.1	27.1	49.7	47.8
8’/2”,6”	–	–	21.0	20.9	32.7	32.5
9’/3”,5”	–	–	16.8	16.8	24.7	24.7
10’/4”	–	–	22.3	22. 3	25.5	25.5

of 2,5-norbornadiene with methyl acrylate as an *E*/*Z* mixture.[14]

L-menthyl *E*-3-bicyclo[2.2.1]hept-5-en-2-yl-prop-2-enoate (**4a,b**) was prepared as a mixture 3/1 of *endo* and *exo* isomers from the acid **2**.[15] *N,N’*-dicyclohexylcarbodiimide (DCC) (2.70 g, 13.2 mmol in dry CH_2Cl_2) was added with stirring at room temperature to a solution of *E*-3-(bicyclo[2.2.1]-hept-5-ene)-prop-2-ene-1-carboxylic acid (1.595 g, 9.85 mmol), L-menthol (1.568 g, 10.10 mmol) and 4-dimethyloaminopyridine (0.742 g, 6.10 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 (Na_2SO_4) and the product obtained after evaporation of the solvent was purified by flash chromatography on silica gel using mixtures of hexane-ethyl acetate as the mobile phase. The first fractions gave the expected methyl ester **4** as a yellowish wax (60-65%); IR (KBr) ν/cm^{-1} 3063, 1708, 1647, 1626, 1577, 1540, 1454, 1390, 1369, 1333, 1230, 1205, 826, 770, 721, 705; ^{1}H and ^{13}C NMR see Tables 1 and 2; HRESIMS calcd. for $C_{20}H_{30}O_2Na$: 325.2144, found: 325.2151. The next fractions afforded a side product 1-[(2*E*)-3-{bicyclo[2.2.1]hept-5-en-2-yl}prop-

2-enoyl]-1,3-dicyclohexylurea (**5a,b**) as a colorless soft glass (20-25%); IR (KBr) ν/cm^{-1} 3280, 3180, 3060, 1702, 1657, 1630, 1530, 1451, 1380, 1340, 1230, 825, 720; ^{1}H and ^{13}C NMR see Tables 1 and 2; ESIMS *m/z* 393; HRESIMS calcd. for $C_{23}H_{34}O_2N_2Na$: 393.2518, found: 393.2514.

Cycloaddition reaction of dipolarophiles **3**-**5** with 4-trifluoromethylbenzonitrile oxide (**6**)

Preparation of compounds **7a,b**-**11a,b** - general procedure

4-Trifluoromethylbenzonitrile oxide was generated as follows: a solution of the corresponding chloroxime (0.57 g, 3.1 mmol) in dry dichloromethane was passed through an Amberlyst-21 column and added dropwise over 20 min to the solution of methyl *E*-3-(bicyclo[2.2.1]-hept-5-ene)-2-propene-1-carboxylate (**3**) 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 (Na_2SO_4) and the product was purified by flash column chromatography on silica gel using mixtures of hexane-ethyl acetate as eluents. Two fractions **7a**, **8a** and **7b**, **8b** were obtained with an overall yield of 78-80%.

Methyl (2*E*)-3-{5-[4-(trifluoromethyl)phenyl]-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-en-9-yl}prop-2-enoate (**7a**): IR (KBr) ν/cm^{-1} 3070, 1724, 1654, 1620, 1598, 1560, 1530, 1450, 1215, 830, 770, 750, 700; ^{1}H and ^{13}C NMR see Tables 3 and 4; ESIMS *m/z* 366 (MH^+), 388 (M^+ + Na); HRESIMS calcd. for $C_{19}H_{18}O_3NF_3Na$: 388.1136, found: 388.1125.

Methyl (2*E*)-3-{5-[4-(trifluoromethyl)phenyl]-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl}prop-2-enoate (**8b**): IR (KBr) ν/cm^{-1} 3065, 1724, 1654, 1620, 1597, 1560, 1450, 1325, 1280, 825, 780, 750, 705; ^{1}H and ^{13}C NMR see Tables 5-6.

5-Methyl-2-(propan-2-yl)cyclohexyl (2*E*)-3-{5-[4-(trifluoromethyl)phenyl]-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-en-9-yl}prop-2-enoate (**9a**): IR (KBr) ν/cm^{-1} 3060, 1710, 1651, 1619, 1593, 1561, 1456, 1325, 1265, 823, 775, 734; ^{1}H and ^{13}C NMR see Tables 3 and 4; MS ESIMS *m/z* 512 (M^+ + Na); HRESIMS calcd. for $C_{28}H_{34}O_3NF_3Na$: 512.2388, found: 512.2394.

1,3-Dicyclohexyl-3-(2*E*)-3-{5-[4-(trifluoromethyl)phenyl]-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-en-9-yl}prop-2-enoyl] urea (**11a**, **11b**): IR (KBr) ν/cm^{-1} 3323, 3080, 1701, 1660, 1620, 1523, 1450, 1375, 1260, 1230, 825, 790, 780, 740, 700; ^{1}H and ^{13}C NMR see Tables 3 and 4; ESIMS *m/z* 580; HRESIMS calcd for $C_{23}H_{34}O_2N_2Na$: 580.2763, found: 580.2772.

Fungicidal testing

The compounds were screened for fungicidal activity *in vitro*. The test was carried out for *Fusarium culmorum* Sacc., *Phytophthora cactorum* Schroek, *Alternaria alternata* Keissl.(Fr.), *Rhizoctonia solani* Kuhn, and *Botrytis cinerea* Pers. Ex Fr, which 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 μg mL^{-1} 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.

Results and Discussion

Structural analysis of the dipolarophiles

The 1,3-dipolar cycloaddition of 4-(trifluoromethyl) benzonitrile oxide (**6**) to norbornenes substituted with the acrylate group **3**, **4** and an unsaturated urea derivative **5** was examined. The compounds described in this work are presented in Scheme 1 and Figure 1. ^{1}H and ^{13}C NMR chemical shifts of the dipolarophiles are shown in Tables 1 and 2, respectively. ^{1}H NMR chemical shifts and multiplicities of adducts **7a,b**-**12a** are shown in Tables 3 and 5. ^{13}C NMR chemical shifts of adducts **7a,b**-**11a,b** are shown in Tables 4 and 6. *Endo* and *exo* configurations of the norbornene side chain in the dipolarophiles **3**, **4** and **5** were established by application of 1D and 2D NMR spectroscopy. The ratio of the C4 epimers was ca. 3:1 and was preserved in the cycloaddition products, which facilitated their structural assignments. In the major *endo* epimer **3a**, the exocyclic olefinic protons gave signals at 6.82 and 5.79 ppm with a large coupling constant of 15.6 Hz proving their *E*-configuration. The position of the crucial H4 proton (multiplet at 2.85 ppm) was fixed by observing a correlation in the 2D COSY spectra with the adjacent olefinic H3 and H5 protons, and a correlation with C4 at 41.88 ppm in the HSQC spectrum. Bridgehead H5 and H8 were multiplets at 2.91 ppm correlated in the COSY spectrum with H4 and H9 protons, respectively, and with C2 at 47.82 and C5 at 42.80 ppm in the HSQC spectrum. In the minor *exo* isomer **3b**, H4 absorbed

Table 3. ^{1}H NMR signals δ of the *anti* adducts **7a,b** and **9a,b** (in acetone-d_6, *J* in Hz), and **11a,b** (in $CDCl_3$; *J* in Hz)

H	7a	7b	9a	9b	11a	11b
2	5.85 (dd, 15.5, 1.2)	6.00 (dd, 15.7, 1.5)	5.97 (dd, 15.7, 1.5)	5.84 (dd, 15.6, 1.5)	6.22 (dd, 15.0, 1.5)	6.24 (d, 15.1)
3	6.90 (dd, 15.5, 7.7)	7.15 (dd, 15.7, 7.3)	7.04 (dd, 15.7, 6.5)	6.88 (dd, 15.6, 7.8)	6.92 (dd, 15.0, 7.3)	7.04 (dd, 15.1, 6.8)
4	2.66 (m)	2.88 (m)	2.89 (m)	2.66 (m)	2.79 (m)	2.77 (m)
5	2.63 (m)	2.74 (bd, 4.3)	2.74 (bs)	2.64 (m)	2.77 (m)	2.70 (d, 4.8)
6	4.79 (d, 8.3)	4.85 (d, 8.4)	4.84 (d, 8.3)	4.79 (d, 8.4)	4.90 (d, 8.2)	4.67 (d, 8.4)
7	3.92 (d, 8.3)	3.92 (d, 8.4)	3.91 (d, 8.3)	3.92 (d, 8.4)	3.57 (d, 8.2)	3.78 (d, 8.4)
8	2.52 (bs)	2.61 (bd, 4.1)	2.59 (d, 4.3)	2.52 (d, 5.6)	2.56 (d, 3.8	2.54 (d, 3.0)
9	1.67, 1.49 (m)	1.98, 1.51 (m)	1.98, 1.50 (m)	1.69, 1.49 (m)	1.97, 1.33 (m)	1.94, 1.06 (m)
10	1.46, 1.41 (m)	1.51, 1.44 (m)	1.50. 1.44 (m)	1.45, 1.40 (m)	1.63, 1.40 (m)	1.63, 1.40 (m)
1’	3.71 (s)	3.74 (s)	4.75 (m)	4.72 (m)	4.04 (m)	4.10 (m)
2’	–	–	1.44 (m)	1.45 (m)	1.83, 1.33 (m)	1.97, 1.26 (m)
3’	–	–	1.71, 1.12 (m)	1.69, 1.10 (m)	1.63, 1.16 (m)	1.63, 1.20 (m)
4’	–	–	1.71, 0.91 (m)	1.69, 0.90 (m)	1.90, 1.80 (m)	1.90, 1.80 (m)
5’	–	–	1.44 (m)	1.49 (m)	1.63, 1.16 (m)	1.63, 1.20 (m)
6’	–	–	1.98, 1.02 (m)	1.94, 0.99 (m)	1.83, 1.31 (m)	1.97, 1.26 (m)
7’/1”	–	–	1.90 (m)	1.86 (m)	3.74 (m)	3.74 (m)
8’/2”, 6”	–	–	0.91 (d, 7.0)	0.90 (d, 7.2)	1.97, 1.26 (m)	1.97, 1.26 (m)
9’/3”, 5”	–	–	0.78 (d, 6.9)	0.75 (d, 7.2)	1.74, 1.40 (m)	1.74, 1.40 (m)
10’/4”	–	–	0.89 (d, 6.9)	0.88 (d, 6.0)	1.90, 1.80 (m)	1.90, 1.80 (m)
2”’, 6”’	8.01 (d, 8.1)	7.89 (d, 8.1)	8.00 (d, 8.3)	7.82 (d, 8.4)	7.82 (d, 8.1)	7.76 (d, 8.1)
3”’, 5”’	7.79 (d, 8.1)	7.79 (d, 8.1)	7.79 (d, 8.3)	7.78 (d, 8.4)	7.66 (d, 8.1)	7.66 (d, 8.1)

Table 4. ^{13}C NMR signals δ of the *anti* adducts **7a,b** and **9a,b** (in acetone-d_6, *J* in Hz), and **11a,b** (in $CDCl_3$; *J* in Hz)

C	7a	7b	9a	9b	11a	11b
1	167.1	166.8	166.1	166.0	165.6	165.6
2	120.6	123.0	123.3	120.5	123.5	123.5
3	152.7	150.4	150.1	151.5	147.4	147.5
4	42.9	39.8	39.9	42.0	48.7	41.2
5	45.1	49.4	49.5	43.5	40.3	44.0
6	88.1	85.5	85.5	88.1	84.7	88.0
7	57.2	57.1	57.2	56.4	57.0	51.0
8	44.4	41.2	41.3	44.2	39.3	44.5
9	30.5	33.1	34.2	29.9	33.3	28.8
10	30.4	34.9	33.2	29.5	33.8	33.7
11	156.2	156.8	156.9	156.9	155.9	156.1
1’	51.5	51.5	74.2	73.3	55.8	55.8
2’	–	–	48.0	47.1	26.2	32.7
3’	–	–	24.2	23.3	25.4	25.5
4’	–	–	35.0	34.0	30.9	31.0
5’	–	–	32.2	31.3	25.4	25.5
6’	–	–	41.8	41.0	26.2	32.7
7’/1”	–	–	27.1	26.2	50.0	50.1
8’/2”,6”	–	–	21.0	21.4	32.8	32.7
9’/3”,5”	–	–	16.8	15.8	24.7	24.7
10’/4”	–	–	22.3	20.1	31.0	31.1
1”’		134.4	134.3	131.9	132.6	132.5
2”’, 6”’	128.2	128.2	128.2	127.4	127.0	127.1
3”’, 5”’	126.5 (q, 3.4)	126.5 (q, 3.9)	126.6 (q, 2.9)	125.6 (q, 3.8)	125.8 (q, 3.6)	125.9 (q, 3.6)
4”’	131.4 (q, 32.0)	131.5 (q, 32.4)	131.5 (q, 32.8)	131.9 (q, 32.8)	131.6 (q, 32.7)	131.5 (q, 32.5)
CF_3	125.0 (q, 240.0)	125.1 (q, 271.6)	125.0 (q, 222.3)	124.6 (q, 272.0)	123.9 (q, 272.2)	123.9 (q, 272.0)

Table 5. ^{1}H NMR signals δ of the *syn* adducts **8a,b**, **10a,b** (in acetone-d_6, *J* in Hz), and **12a** (in $CDCl_3$; *J* in Hz)

H	8a	8b	10a	10b	12a
2	5.86 (dd, 15.5, 1.2)	5.97 (dd, 15.7, 1.6)	6.00 (dd, 15.7, 1.4)	5.81 (dd, 15.5, 0.5)	6.09 (dd, 14.9, 1.0)
3	6.88 (dd, 15.5, 7.7)	7.03 (dd, 15.7, 7.1)	7.17 (dd, 15.7, 6.3)	6.86 (dd, 15.5, 7.5)	6.81 (dd, 14.9, 8.1)
4	2.44 (m)	2.87 (m)	2.88 (m)	2.30 (m)	2.45 (m)
5	2.50 (m)	2.65 (bd, 3.2)	2.67 (d, 3.2)	2.59 (d, 3.5)	2.76 (d, 3.0)
6	3.85 (d, 8.4)	3.93 (d, 8.4)	3.93 (d, 8.3)	3.57 (d, 8.0)	3.59 (d, 8.4)
7	4.83 (d, 8.4)	4.78 (d, 8.4)	4.76 (d, 8.3)	4.77 (d, 8.0)	4.74 (d, 8.4)
8	2.63 (m)	2.59 (bd, 5.1)	2.61 (d, 4.8)	2.63 (bs)	2.72 (d, 4.5
9	1.88, 1.51 (m)	1.94, 1.19 (m)	1.93, 1.20 (m)	1.76, 1.51 (m)	1.94, 1.30 (m)
10	1.44, 1.41 (m)	1.51, 1.44 (m)	1.52. 1.46 (m)	1.51, 1.42 (m)	1.60, 1.44 (m)
1'	–	–	4.76 (m)	4.75 (m)	4.02 (m)
2'	–	–	1.46 (m)	1.42 (m)	1.81, 1.30 (m)
3'	–	–	1.71, 1.14 (m)	1.69, 1.08 (m)	1.60, 1.18 (m)
4'	–	–	1.71, 0.92 (m)	1.69, 0.90 (m)	1.94, 1.81 (m)
5'	–	–	1.52 (m)	1.51 (m)	1.60, 1.18 (m)
6'	–	–	1.99, 1.03 (m)	2.01, 1.00 (m)	1.81, 1.30 (m)
7'/1''	–	–	1.93 (m)	1.87 (m)	3.70 (m)
8'/2'', 6''	–	–	0.92 (d, 7.2)	0.90 (d, 7.0)	1.94, 1.24 (m)
9'/3'', 5''	–	–	0.80 (d, 6.6)	0.77 (d, 7.0)	1.69, 1.44 (m)
10'/4''	–	–	0.92 (d, 7.2)	0.91 (d, 6.5)	1.94, 1.81 (m)
2''', 6'''	7.99 (d, 8.2)	8.00 (d, 8.0)	7.88 (d, 8.2)	7.82 (d, 8.3)	7.79 (d. 7.8)
3''', 5'''	7.77 (d, 8.2)	7.78 (d, 8.0)	7.77 (d, 8.2)	7.66 (d, 8.3)	7.64 (d, 7.8)

Table 6. ^{13}C NMR signals δ of the *syn* adducts **8a,b** and **10a,b** (in acetone-d_6, *J* in Hz)

C	8a	8b	10a	10b
1	167.1	166.9	166.0	166.2
2	120.5	122.4	123.7	120.9
3	152.2	150.4	150.2	150.3
4	38.7	41.9	42.0	38.1
5	49.3	45.2	45.2	33.6
6	56.8	51.5	51.6	56.5
7	88.8	88.9	89.0	88.0
8	40.6	44.9	44.9	48.1
9	35.1	28.8	28.6	34.8
10	30.5	34.1	34.0	30.2
11	156.8	156.7	156,7	155.8
1'	51.5	51.5	74.3	74.2
2'	–	–	48.0	47.1
3'	–	–	24.4	23.6
4'	–	–	35.0	34.3
5'	–	–	32.1	31.5
6'	–	–	41.9	41.0
7'	–	–	27.3	26.4
8'	–	–	21.0	20.7
9'	–	–	16.9	16.5
10'	–	–	22.4	22.0
1'''	134.3	134.3	134.3	132.5
2''', 6'''	128.2	128.5	128.0	127.0
3''', 5'''	126.5 (q, 3.4)	126.5 (q, 3.9)	126.6 (q, 4.1)	125.7 (q, 3.4)
4'''	131.4 (q, 32.6)	131.3 (q, 32.6)	131.4 (q, 32.9)	131.6 (q, 32.7)
CF_3	125.0 (q, 272.0)	125.1 (q, 272.0)	125.1 (q, 269.0)	123.8 (q, 271.9)

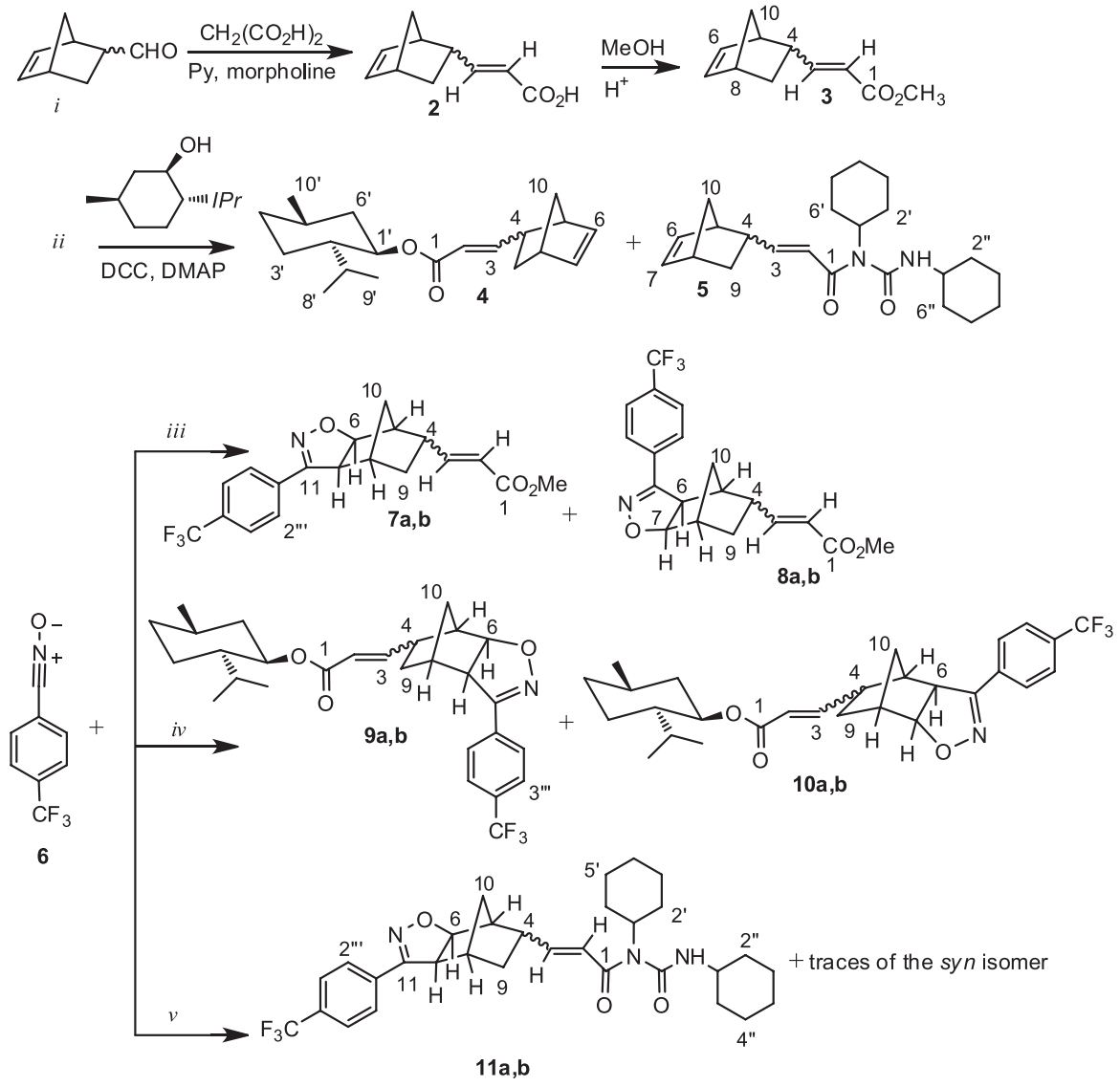
at 2.18 ppm showing correlations with H3 and H9 protons (1.42 and 1.38 ppm) in the COSY spectrum, and with C4 (41.46 ppm) in the HSQC spectrum. *Endo* configuration of **3a** was proved by the position of C10 signal at lower field (49.61 ppm), and C8 signal at higher field (42.80 ppm) than that in the *exo* epimer (at 45.47 and 47.75 ppm, respectively) because of the γ-effect of the side chain.

Structures of the other two dipolarophiles **4** and **5** were similarly established.

Structural analysis of the cycloadducts

The cycloaddition of 4-trifluoromethylbenzonitrile oxide to the olefin **3** afforded two pairs of diastereoisomers which were separated by column chromatography. In the first pair (**7a**, **8a**), the side chain was in *endo* configuration, and in the second pair (**7b**, **8b**), the side chain was in *exo* configuration. Cycloaddition to the menthyl ester **4** yielded separable diastereoisomers **9a**, **9b** and **10a**, **10b**, and reaction with the urea derivative **5** gave mainly *anti* adducts **11a**, **11b** (*vide supra*) as well as very small amounts of *syn* isomers **12a,b** (not shown).

Only adducts to the norbornenesystem were formed with a complete site-selectivity and *exo* selectivity which was proved by coupling pattern of H6 and H7 in the ^{1}H NMR spectra. Both protons were doublets coupled only to each other (*J* 8.0-8.4 Hz). Coupling constants with the adjacent *endo* bridgehead protons H5 and H8 are very small



Scheme 1. Cycloaddition products of the dipole **6** to the dipolarophiles **3**, **4**, **5**.

(0-1 Hz) which corresponds to the value of the respective dihedral angles close to 90°.[5]

Regiochemistry of the cycloadducts was established by ^{1}H NMR and 2D NMR NOESY spectroscopy (Figure 1). In compounds **7a,b**, **9a,b** and **11a,b** with a*nti* relationship of the phenyl ring and the methylene bridge, H6 showed cross peak with H5, and H7 showed cross peak with H8. On the other hand, in the regioisomeric cycloadducts **8a,b** and **10a,b** with *syn* relationship of the phenyl ring and the methylene bridge, the corresponding H7 exhibited cross peak with H8, and H6 exhibited cross peak with H5 [cf 6]. In all, the *anti* adducts H5 in the vicinity of two electron-withdrawing bonds (C–O and C=C) showed larger chemical shifts than H8 as well as H5 in the *syn* regioisomer. The relevant 2D COSY, HMBC and NOESY correlations supporting structure elucidation for the diastereoisomers **7a**, **10a,b** and **11a** are shown in Figure 1.

Rationalization of the observed site-selectivity and regioselectivity

Calculations of electron charges on alkenyl atoms C2, C3 as well as C6 and C7 of the dipolarophiles **3**-**5** with the Hyperchem 7.5 program using the semiempirical AM1 method showed higher total electron densities at C6-C7 double bond, than at the more polarized conjugated C2-C3 bond (Table 7). This difference is probably responsible for the selective cycloaddition to the norbornenyl moiety.

The regioselectivity of the cycloaddition to this fragment is more difficult to explain. The difference of the negative charges between C5 and C6 is small and variable; only for the dipolarophile **4** the norbornene double bond polarization is consistent with the observed regioselectivity. The major *syn* isomer is formed via

Table 7. Electron charges at the alkenyl carbon atoms of the dipolarophiles **3**-**5** (*endo* isomers) and *anti*/*syn* regioselectivity in the cycloaddition reaction

Dipolarophile/C atom	C2	C3	C6	C7	Regioselectivity	
					endo	*exo*
3	–0.207	–0.054	–0.173	–0.170	4:1	4:1
4	–0.212	–0.054	–0.179	–0.189	2:1	2.5:1
5	–0.228	–0.087	–0.179	–0.170	1.9:1	1.5:1

Table 8. Fungicidal inhibitory activities of compounds **3a,b**, **4a,b**, **7a,b**, **8a,b** and **11b** at 200 μg mL^{-1} [a]

Compound	**3a,b**	**4a,b**	**7a, 8b**	**7b, 8a**	**11b**	Chlorothalonil
Botrytis cinerea	16	0	100	18	73	80
Fusarium culmorum	0	5	0	19	60	38
Rhizoctonia solani	31	22	100	42	44	88

[a]Percentage of linear growth inhibition.

oxygen atom of the dipole attacking the less negatively charged C5 atom of the dipolarophile. Other factors, such as orbital control and steric interactions, have to be considered, apart from stereoelectronic effects. Although generally regarded as weak,[16] orbital control determines the observed regiochemistry of cycloaddition of nitrile oxides to acrylates and methacrylates overruling the steric and stereoelectronic factors.[2] Cycloaddition to norbornenes, an electron-rich system, is controlled by $LUMO_{dipol}$-$HOMO_{alkene}$ interaction since $LUMO_{alkene}$-$HOMO_{dipol}$ energy gap is higher.[17] Regioselectivity of the reaction is determined by the values of the atomic orbital coefficients of the olefinic carbon atoms. However, differences of FMO (frontier molecular orbital) coefficient values for sp^2 carbon atoms published for similar systems, 2-substituted norbornadienes, are too small to be a decisive factor.[18] These results suggest that secondary orbital interactions are a plausible source of the regioselectivity. A similar conclusion was reached by Kurita and Takayama,[19] who examined electrophilic additions to norbornene. Our group did not find any positive remote group effect of the menthyl ester on regioselectivity of the cycloaddition rection compared to the results obtained for the methyl ester (Table 7), in which the observed level of regioselectivity decreased from 80:20 to 66:34. Such remote substituent effects were, on the other hand, recently reported in the Pauson-Khand [2 + 2 + 1] cycloaddition of 2-substututed-5-norbornenes.[6]

Biological activity of the cycloadducts

The biological activity of the compounds **7a**-**12b** against several fungal strains was examined. Preliminary assays showed high fungistatic potency of cycloadducts **7a**, **8a** pair against *Botrytis cinerea* and *Rhizoctonia solani* (100% growth retardation at 200 mg L^{-1} concentration) which was most active of all the tested compounds (Table 8). The reference compound (chlorothalonil) showed 80 and 88% activities against these strains, respectively.

Conclusions

The 1,3-dipolar cycloaddition of 4-trifluoromethyl-benzonitrile oxide to alkenyl-substituted norbornenes shows site-selectivity and occurs only to the norbornene system with *exo* selectivity and moderate to good regioselectivity presumably because of the higher electron densities at these positions. Regioselectivity of the reaction, in which *anti* isomers were dominant, was established by comprehensive analyses of ^{1}H NMR and 2D NOESY spectra. All diastereoisomeric products were fully characterized by ^{1}H and ^{13}C NMR 1D and 2D spectroscopy. Some cycloadducts showed promising biological activity. Further research is in progress to analyze the biological potency of the new products and to improve regioselectivity of the cycloaddition reaction.

Supplementary Information

Supplementary data (^{1}H NOESY, COSY, ^{1}H-^{3}C HSQC, ^{1}H-^{3}C HMBC spectra) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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