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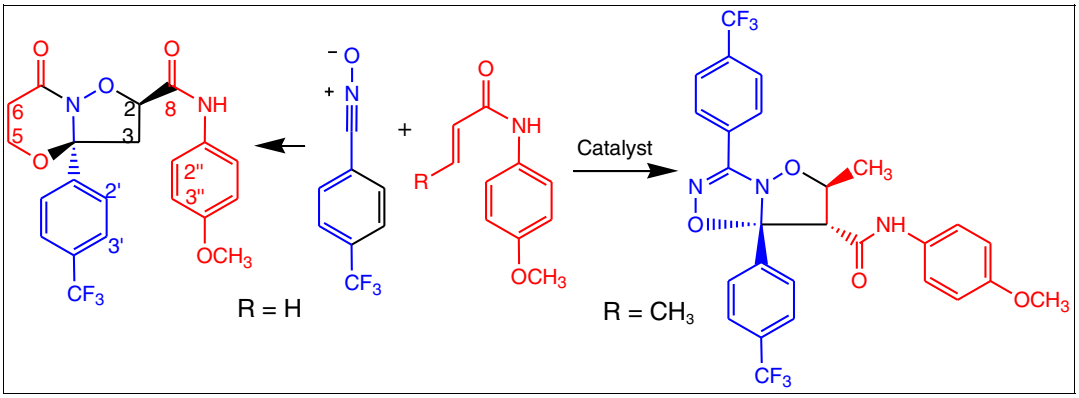

Cycloaddition of (4-trifluoromethyl)phenylnitrile oxide to *N*-(4-methoxyphenyl)acrylamide afforded bicyclic tetrahydro-oxazolo-(3,2-*b*)[1,3]oxazine-2-carboxamide derivative in result of N-acylation of the initially formed cycloadduct by the dipolarophile. 2:1 Cycloaddition of the same dipole to *N*-(4-methoxyphenyl) crotonamide yielded dihydro[1,2]-oxazolo[2,3-*d*][1,2,4]oxadiazole-7-carboxamide because of the second addition of the dipole to the C=N bond of the first formed 2-isoxazoline compound. Structures of the products have been elucidated by an extensive application of 1D and 2D NMR spectroscopy.

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INTRODUCTION

2-Isoxazolines are versatile intermediates in the synthesis of many complex biologically active compounds that can be easily transformed by reductive N–O bond cleavage to several important compounds such as β-hydroxy ketones, β-hydroxy esters, α,β-unsaturated carbonyl compounds, or iminoketones [1]. The most useful method of 2-isoxazoline preparation is the 1,3-dipolar cycloaddition reaction of nitrile oxides to alkenes [2]. The nitrile oxides can be formed either by Huisgen method from aldoximes by chlorination and base-induced dehydrochlorination [2] or by Mukayama method from primary nitro compounds and phenyl isocyanates [3]. Diastereoselective and enantioselective cycloadditions have been studied extensively with application of optically active substrates and chiral catalysts [4]. Several obstacles such as propensity of nitrile oxides to dimerize and form unreactive complexes with metal catalysts as well as interaction of tertiary amines used to generate nitrile oxides with Lewis acids had to be overcome [5]. Coordination of amine bases to Lewis acid could be circumvented by, for example, application of Amberlyst 21, a strongly basic ion exchange resin, as a base to generate nitrile oxides from hydroximinoyl chlorides [6].

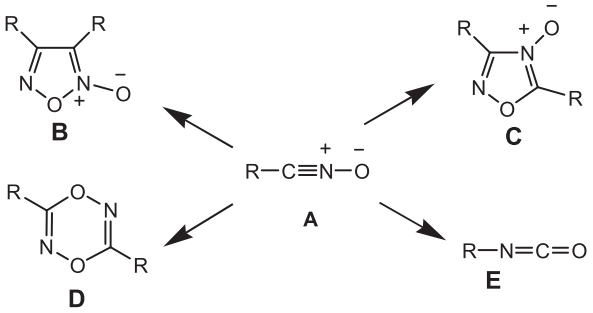
In synthesizing biologically active compounds, it is important to identify the observed side products and competitive reactions pathways negatively influencing yield and purity of the desired substances. There is a relative shortage of data concerning side products in the 1,3-dipolar cycloaddition reaction of nitrile oxides. The only reported side products concern dimerization and other transformations of the dipoles.

Most nitrile oxides are unstable, some of them are explosive. In the absence of dipolarophiles, nitrile oxides **A** easily dimerize at ambient and lower temperatures to give furoxans (1,2,5-oxadiazole 2-oxides) **B**, which are products of the kinetical control [7]. The furoxans are not dead-end side products with regard to cycloaddition but can afford back nitrile oxides by thermolytic cycloreversion [8].

DFT calculations (B3LYP/6.31G*) for acetonitrile oxide and *p*-chlorobenzonitrile oxide have demonstrated that dimerizations were two-step processes involving dinitroso alkene intermediates, and the limiting stage was C–C bond formation [7].

Dimerization routes are shown in Scheme 1 [9]. Under basic (trimethylamine, triethylamine, or pyridine) [10–12] or acidic conditions (excess of BF_3) [13,14], dimerizations can give also 1,2,4-oxadiazole 4-oxides **C** more thermodynamically stable than furoxans or 1,4,2,5-dioxadiazines **D**[7], which are usually regarded as minor products [9]. Isocyanates **E** can be formed only at elevated temperatures; this is the main reaction of sterically stabilized nitrile oxides.

Scheme 1. Dimerization and isomerization of nitrile oxides.



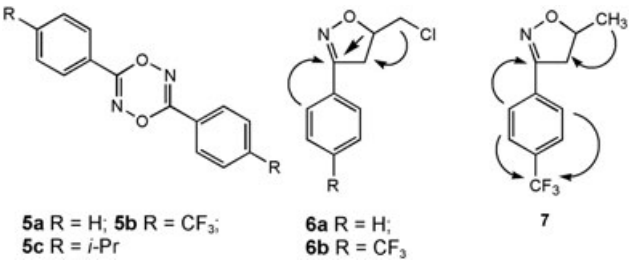


Figure 1. Minor side products shown with selected HMBC correlations.

We carried out many cycloaddition reactions of 21 nitrile oxides to two unsaturated alcohols, 14 esters, and 12 amides mediated by complexes of lanthanides and other Lewis acids with chiral ligands obtaining products with variable regioselectivities and enantioselectivities up to 99%, including several biologically active carboxamides [15–18]. Herein, we wish to present the results of a thorough analysis of the reaction mixtures that showed the presence of several side products, some of which were quite unexpected and interesting from the synthetic point of view. It led to the discovery of novel 2-isoxazoline N-acylation by *N*-alkenylamide.

RESULTS AND DISCUSSION

We have recently examined the cycloaddition reaction of benzonitrile oxides **1a–c** with α,β-unsaturated amides **2a,b** and have obtained products **3–4** (Scheme 2).

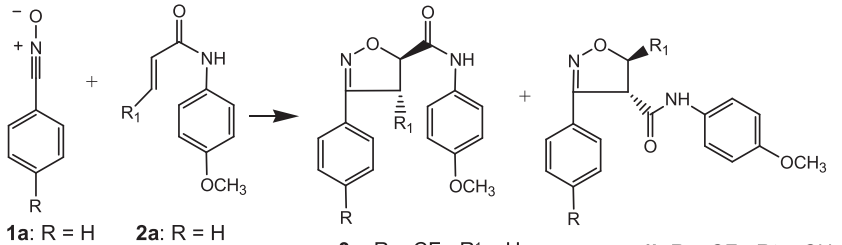
All the reaction mixtures contained, similarly as in our previous studies, small amounts of nitrile oxide dimers (2–3%) that were isolated and analyzed by spectral methods. Our results showed, on the contrary to the literature data, that they are not furoxans, but rather 1,4.2.5-dioxadiazines **5a–c** (Fig. 1). ^{1}H NMR spectrum of (4-trifluoromethyl) phenyl nitrile oxide dimer shows only two multiplets corresponding to the symmetrical 2,4-di(4-trifluoromethyl) phenyl)-1,4,2,5-dioxadiazine (**5b**). If this nitrile oxide dimer had a furoxan structure **B** or 1,2,4-oxadiazole 4-oxide structure **C**, then at least three multiplets would be expected. The same NMR behavior was observed for the other two products—unsubstituted benzonitrile oxide dimer **5a** and (4-*iso*propyl)phenylnitrile oxide dimer **5c**.

The first new side products observed by us were 5-chloromethyl-3-aryl-4,5-dihydro-isoxazoles **6a**,**b** (Fig. 1) formed in the 1,3-dipolar cycloaddition reaction of the corresponding benzonitrile oxides with different dipolarophiles run in anhydrous methylene chloride with Amberlyst (Rohm and Haas, Germany) 21 as a base to generate dipoles from hydroximinochlorides. Structures of both products were established by spectral methods. High-resolution (HR) EIMS of **6a**, isolated in cycloaddition of **1a** dipole, showed the composition $^{35}C_{10}H_{10}ClNO$. The ^{1}H NMR spectrum exhibited five aromatic protons, one proton multiplet at δ 4.99, two one-proton geminally coupled doublets at δ 3.72 and 3.58 correlated in HMBC spectrum with δ_C79.8 and 38.6 signals, and two one proton geminally coupled doublets at δ 3.50 and 3.35. This data indicated a 3,5-disubstituted 2-isoxazoline system with a C5-CH_2Cl side group and were confirmed by HSQC and COSY spectra.

The higher molecular weight analogue **6b**, isolated in cycloadditions of **1b** dipole, showed the composition $^{35}C_{11}H_9F_3ClNO$ in HRMS. The ^{1}H and ^{13}C NMR spectra differed only in the aromatic region, and structure of the product was established similarly as previously described.

Both compounds could be formed by the cycloaddition of nitrile oxide to allylic chloride (an unknown artifact). Isoxazoline **6a** was obtained before as the main product in this type of reaction [19].

Scheme 2. Cycloaddition of nitrile oxides to unsaturated amides, the main products.



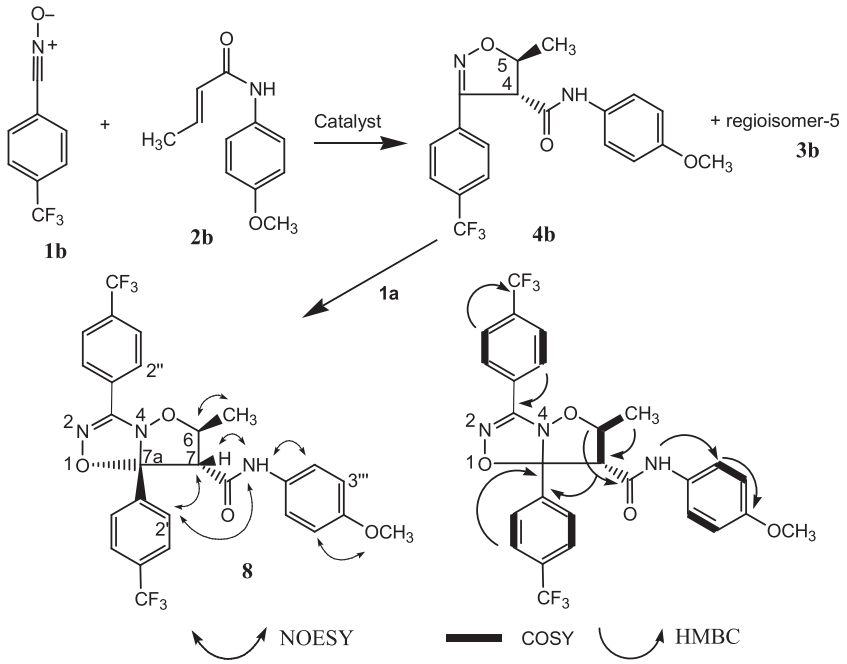
The second side product, isolated in cycloaddition of **1a** dipole, was 5-methyl-3-(4-trifluoromethyl)phenyl-4,5-dihydroisoxazole (**7**) (Fig. 1). HRMS showed the composition $C_{11}H_{10}F_3NO$. The ^{1}H NMR spectrum exhibited a typical pattern of 3,5-disubstituted 2-isoxazoline system, differing from spectra of compounds **6a**,**b** in a larger separation of H4 signals (0.51 ppm compared with 0.15 ppm in **6a**,**b**), and the presence of C5 methyl group was proved by the HSQC correlation of a three H triplet at δ 1.39 with C6 triplet at δ 21.2 in DEPT spectrum.

Compound **7** could be formed in the 1,3-dipolar cycloaddition reaction of (4-trifluoromethyl)phenyl nitrile oxide **1b** with 1-propene. Careful GC–MS analysis of the dichloromethane eluate from Amberlyst 21-filled column showed the presence of this alkene. This result indicated a drawback of the method used to generate nitrile oxides.

The third interesting new side product **8** was isolated in the cycloaddition reaction of (4-trifluoromethyl)phenylnitrile oxide (**1b**) with *N*-(4-methoxyphenyl)crotonamide (**2b**) mediated by the complex of ytterbium triflate with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (Scheme 3). There was neither chiral induction nor regioselectivity in this reaction, on the contrary to the other catalytic systems with different ligands elaborated by us [18], but the overall yield of two regioisomers **3b, 4b** formed in 1:1 ratio was high (90%). The ^{1}H NMR spectrum of the side product **8** showed a resemblance to the spectrum of *N*-(4-methoxyphenyl)-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-carboxamide (**4b**). The difference was the presence of two additional low-field two-proton doublets and an upfield shift of the isoxazoline H5 and H4 signals. Field desorption mass spectroscopy (FD-MS) showed the molecular ion at *m*/*z* 565, corresponding to an increase of molecular weight by 187 mu compared with the carboxamide **4b**. This result indicated an addition of the second dipole unit to the isoxazoline **4b** C=N bond and rationalized an upfield shift of H2 and H3 peaks of the side product **8** (Scheme 3). ^{19}F NMR spectroscopy demonstrated the presence of two fluorine signals at −63.1 and −63.6 ppm, and HR electrospray mass spectroscopy exhibited the quasi-molecular formula as $C_{27}H_{21}N_3O_4F_6Na$. HMBC-^{15}N spectroscopy proved disappearance of *N* signal at −2.7 ppm having cross peak with H4 of isoxazoline **4b** and appearance of a new *N* signal of isoxazolidine **8** at −66.2 ppm correlated with CH_3 protons. The COSY, HSQC, and HMBC correlations confirmed the structure of **8** and enabled the complete assignment of ^{1}H and ^{13}C NMR spectra (see Experimental part). Strong NOE between H7 and H2′ protons indicated their cis relationship; β-orientation of the C7a aromatic ring was assumed on the basis of molecular modeling (the PM3 method).

The recently reported cycloaddition reaction of phosphonyl nitrile oxides and acrylonitrile gave a similar 2:1 cycloaddition product with the trans relationship of C7/C7a substituents [20]. Similar cycloaddition of 4-alkoxyphenylnitrile oxide to vinylacetic acid afforded exclusively a bicyclic 2:1 adduct because of the low dipolarophilic reactivity of the vinylacetic acid in comparison with the initially formed 3,5-disubstituted isoxazoline. Configuration of the product was not established [21].

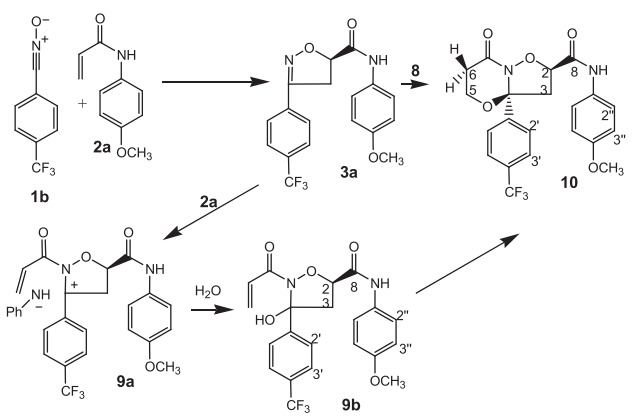
Scheme 3. Formation of the side product **8**. Selected NOEs, COSYs and HMBC correlations observed in **8**.



The next interesting new side product was a bicyclic amide (**10**) formed in the reaction of (4-trifluoromethyl) phenylnitrile oxide (**1b**) with *N*-(4-methoxyphenyl)acrylamide (**2a**) (Scheme 4). ^{1}H NMR spectrum contained all the signals of the expected cycloaddition product, *N*-(4-methoxyphenyl)-3-(4-trifluoromethyl)phenyl-4,5-dihydroisoxazole-5-carboxamide (**3a**), and additionally a two-proton triplet at 2.73 ppm, and a two-proton multiplet at 4.50 ppm. The latter signal collapsed to a triplet with the same coupling (6.1 Hz) as shown by the 2.73 ppm triplet, when the spectrum was recorded in CD_2Cl_2. The 2D NMR COSY spectrum confirmed coupling of these signals as well as the presence of the isoxazolidine system (coupling of H2 with H3 protons). One bond ^{1}H–^{13}C correlation (HSQC) demonstrated cross peaks of H 4.50 multiplet and H 2.73 triplet with carbon 61.5 and 35.6 ppm signals, respectively. The position of the first carbon peak indicated a proximity of an ether function. The HMBC spectrum showed the presence of the second carbonyl group at δ 167.4 exhibiting the cross peaks with H 2.73 and 4.50 ppm signals. IR spectrum confirmed the presence of two carbonyl functions. The first group absorbed at 1668 cm^{-1}, a typical value for secondary acyclic amides. The second peak at 1749 cm^{-1} could be ascribed to ring-fused γ-lactams or α,β-unsaturated δ-lactones [22]. These data suggested the presence of isoxazoline C═N bond annelated six-membered heterocyclic ring and rather a δ-lactam structure. The EI-MS spectrum showed a molecular ion of 436 mu and HR ESI-MS exhibited the quasi-molecular formula as $C_{21}H_{19}F_3N_2O_5Na$ (Scheme 4).

Stereochemistry of this adduct was examined with help of ^{1}H NMR spectroscopy. The striking feature was the chemical equivalence at room temperature spectra of H5 and H6 peaks and a small value of vicinal H5/H6 coupling constant of 6.1 Hz only, not compatible with a rigid chair conformation, where large diaxial coupling constant would be expected for one proton pair. This value of *J* is low even after accounting for the effect of electronegative atoms lowering the coupling constant and corresponds to a dihedral angle of 32° only using modified Karplus equation [23]. Large H2/H3A *J* of 11.8 Hz indicated an antirelationship of these protons. The molecular modeling indicated the boat conformation of six-membered heterocyclic ring after energy optimization using PM3 semi-empirical method. It could be favored because of the diminished bond eclipsing in result of nitrogen atom presence and lack of "flagpole" position atoms at either end of the molecule, occupied by the carbonyl and oxygen atom. Unfortunately, we were unable to determine structure of compound **10** by X-ray crystallography, because of lack of an appropriate crystal form. However, chemical equivalence of H5 and H6 protons and small value of vicinal H5/H6 coupling could indicate rather a rapid equilibrium of several different conformations including a boat, twist-boat, and half-chair, at the NMR time scale. Low-temperature ^{1}H NMR spectra should shed some light on this topic. In the quest to find different "frozen" conformations, we have run ^{1}H NMR spectra in deuterioacetone at −60 to 90°C. Unexpectedly, the only change was a lowered H5/H6 coupling constant from 6.1 Hz at RT to 5.0 Hz at −90°C and a low-field shift of protons in the vicinity of carbonyl groups. This δ shift was particularly pronounced for NH (0.64 ppm). Minor low-field δ shifts were observed for H2 (0.12) and H3A (0.09). This result could be explained by an association of the diamide **10** with the solvent acetone. Such intermolecular interactions of carbonyl compounds are well known [24]. Aggregation of acetone and its derivatives studied by the static dielectric method has recently shown a parallel dipole alignment [25]. In our molecule, the carbonyl dipoles are perpendicular to the long molecular axis, and this would favor a head-to-tail association leading to an increased polarization of both carbonyl groups and a downfield shift of the proximate protons. This aggregation is important already at RT as witnessed by the low-field position of the NH signal at 9.1 ppm in acetone compared with position in CD_2Cl_2 at 7.24 ppm. The observed large negative temperature effect on the aggregation has been recorded in the literature [26,27]. The temperature effect on coupling constant could indicate a conformational bias toward a flexible boat at lower temperatures [28].

Scheme 4. Presumed formation of the side product **10**.



Further information concerning the spatial structure of the product was provided by the ^{1}H NOESY spectrum that unexpectedly showed strong NOE of NH proton with H-6 signal. Another diagnostic NOE was observed for upfield H3A and aromatic H2′/H6′ signals. The correlations indicate spatial proximity of these protons and are shown in Figure 2, displaying one of possible conformations of **10** with cis ring fusion and an envelope conformation of the isoxazolidine ring.

Compound **10** could be envisaged as arising from transformations of a 1:2 adduct. When an experiment was carried out in which a threefold excess of the dipolarophile **2a** was applied, the main product was, as expected, the

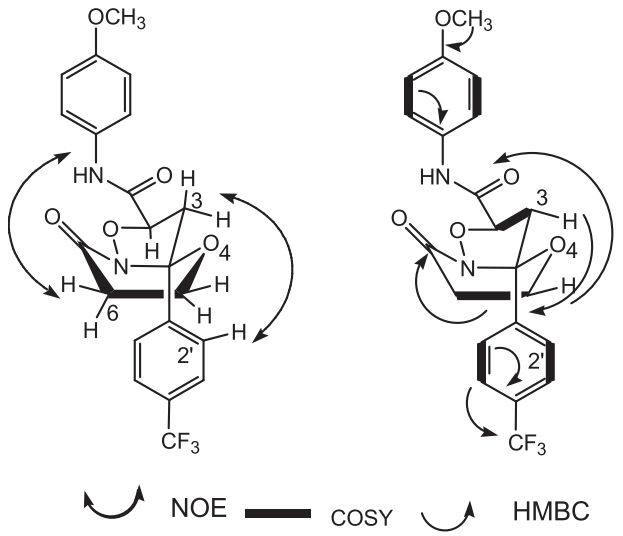


Figure 2. Selected NOEs, COSYs, and HMBC correlations observed in the favored conformation of **10**.

bicyclic derivative **10** isolated in 65% yield. The suggested reaction pathway could involve isoxazoline **3a** N-acylation with the amide **2a** followed by an attack of the nucleophilic water molecule on the intermediate ion pair **9a** and regioselective Michael-type addition of hydroxy group of **9b** to carbon–carbon double bond. Several literature examples are available of amides as acylation agents. *N*-acylpyrroles are active acylation agents in reactions with different nucleophiles [29]. *N*-acylbenzotriazoles are used to efficiently convert Wang resin-linked amines into primary, secondary, and tertiary amides [30]. A twisted amide, 3-pivaloyl-1,3-thiazolidine-2-thione, was a selective acylating agent for diols under neutral conditions [31]. To the best of our knowledge, it is the first example of 2-isoxazoline adduct acylation by the dipolarophile of an *N*-alkenyl amide type.

A literature search of the isoxazolo-oxazinone systems has turned our attention to the related structure of 3,3a-dihydro-2*H*,9*H*-isoxazolo[3,2-*b*]benzooxazin-9-ones (**11**) (Fig. 3) that exhibited good anti-inflammatory activity, low toxicity, and virtually no gastric irritation [32]. Our method of synthesis could provide an alternative excess to the analogues of this valuable heterocyclic system.

CONCLUSION

A careful analysis of reaction mixtures obtained in the 1,3-dipolar cycloaddition reaction of nitrile oxides to unsaturated amides revealed the presence of several side products. The most interesting derivative *N*-(4-methoxyphenyl)-7-oxo-3a-[4-(trifluoromethyl)phenyl]tetrahydro-2*H*,5*H*-[1,2]oxazolo[3,2-*b*][1,3]oxazine-2-carboxamide **(10)** could be obtained as the main product when reaction conditions

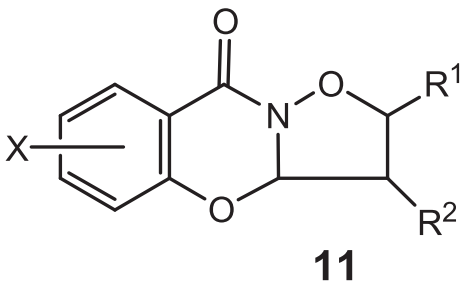


Figure 3. Biologically active isoxazolidino[3,2-*b*]benzooxazin-9-ones.

were modified. It originated from the coupling of two *N*-(4-methoxyphenyl)acrylamide units with (4-trifluoromethyl) benzonitrile oxide (**1b**). Its formation constitutes the first example of 2-isoxazoline derivative N-acylation by *N*-alkenylamide. Preparation of **10** may be considered as an alternative approach to the synthesis of the known valuable anti-inflammatory compounds such as **11**. The other unusual novel product –arylo-dihydro[1,2]oxazolo[2,3-*d*][1,2,4]oxadiazole-7-carboxamide **8** derivative was formed by successive cycloaddition of two (**1b**) dipole moieties with one dipolarophile unit. Further research is in progress to find the scope of the reactions and to analyze the biological activity of the new products.

EXPERIMENTAL

Reagent grade chemicals were used without further purification unless otherwise noted. Elemental analyses were performed on Elementar Vario (Warsaw, Poland) EL III apparatus. Spectra were obtained as follows: IR spectra on JASCO (Warsaw, Poland) FTIR-420 spectrometer; ^{1}H NMR spectra on Varian (Warsaw, Poland) 200 UNITY plus-200, Varian 500 UNITY plus-500, and Varian VNMRS 600 spectrometers in deuterated chloroform or acetone using TMS as internal standard; EI mass spectra on AMD M-40, ESI mass spectra on LCT (Micromass, Warsaw, Poland); and FD mass spectra on GCT Premier. Flash chromatography was carried out using silica gel S 230-400 mesh (Merck, Darmstadt, Germany). Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and NCS in DMF [33].

Typical procedure for the cycloaddition of nitrile oxides to unsaturated amides. A mixture of (+)-(4,6-benzylidene) methyl-α-D-glucopyranoside (1.0 mmol) and $Yb(OTf)_3$ (1.0 mmol) in dry dichloromethane was stirred at RT for 30 min. Dipolarophile *N*-(4-methoxyphenyl)acrylamide) (**2a**) (1 mmol) was added dropwise followed by a solution of the dipole in the same solvent generated by passing a hydroximinoyl chloride solution (1.3 mmol) through a column of Amberlyst 21 over 20–30 min. The solution was stirred at RT for about 19 h, water was added to quench the reaction, the reaction mixture was extracted with a brine and dried (Na_2SO_4), and the crude product obtained after evaporation of the solvent *in vacuo* was purified by flash column chromatography on silica gel using gradient of hexanes–ethyl acetate mixtures as an eluent.

***N*-(4-Methoxyphenyl)-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxamide (3a)**. It was obtained in 60% yield [18] as a wax.

***N*-(4-Methoxyphenyl)-4-methyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxamide (3b)** [18]. It was obtained in 45% yield as a wax. ^{1}H NMR (acetone, 200 MHz) δ: 9.13 (bs, 1H, NH), 8.03 (d, J = 8.4 Hz, 2H, H6′, H2′), 7.82 (d, J = 8.4 Hz, 2H, H5′, H3′) 7.68 (d, J = 9.1 Hz, 2H, H″, H6″), 6,87 (d, J = 9.1 Hz, 2H, H3″, H5″), 4.94 (d, J = 4.2 Hz, 1H, H5), 4.28 (qd, J = 7.2: 4.2 Hz, 1H, H4), 3.76 (s, 3H, CH_3O), 1.43 (d, J = 7.2 Hz, 3H, CH_3); ^{15}N NMR (acetone, 600 MHz from HMBC) δ: −11.2 (s, N2), −257.2 (d, J = −100 Hz, HNC═O); HR ESI-MS Calcd for $C_{19}H_{17}N_2O_3F_3Na$ 401.1089, found 401.1077.

***N*-(4-Methoxyphenyl)-3-(4-isopropylphenyl)-4-methyl-4,5-dihydroisoxazole-5-carboxamide (3c)**. It was obtained as a white-brownish semisolid in 8% yield [18].

***N*-(4-Methoxyphenyl)-5-methyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-carboxamide (4b)**. It was obtained in 45% yield as a wax. ^{1}H NMR (acetone, 600 MHz) δ: 9.68 (s, 1H, NH), 7.94 (d, J = 8.2 Hz, 2H, H5′, H3′), 7.75 (d, J = 8,2 Hz, 2H, H2′, H6′), 7.52 (d, J = 9.0 Hz, 2H, H2″, H6″), 6.86 (d, J = 9.0 Hz, 2H, H5″, H3″), 5.08 (qd, J = 7.0; 6.6 Hz, 1H, H5), 4.46 (d, J = 7.0 Hz, 1H, H4), 3,75 (s, 3H, CH_3O), 1.51 (d, J = 6.6 Hz, 3H, CH_3); ^{15}N NMR (acetone, 600 MHz from HMBC) δ: −2,7 (s, N2) (H4), −249.2 (d, J = −100 Hz, HNC═O) (HN, H2″, H6″).

***N*-(4-Methoxyphenyl)-3-(4-isopropylphenyl)-5-methyl-4,5-dihydroisoxazole-4-carboxamide (4c)**. It was obtained as a yellowish semisolid in 32% yield [18].

3,6-Diphenyl-1,4,2,5-dioxadiazine (5a). It was obtained as a brownish wax. IR (KBr) 3075, 1595, 1575, 1502, 1421, 774, 693, 655; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.50 (m, 4H), 7.45 (m, 6H).

3,6-Bis[4-(trifluoromethyl)phenyl]-1,4,2,5-dioxadiazine (5b).It was obtained as a brownish wax. IR (KBr) 1595, 1407, 1327, 1133, 845; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.76 (d, J = 8.3 Hz, 2H, H2′, H6′), 7.65 (d, J = 8.9 Hz, 2H, H5′, H3′).

3,6-Bis[4-(propan-2-yl)phenyl]-1,4,2,5-dioxadiazine (5c). It was obtained as a brownish wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.48 (dd, J = 8.5; 2.0 Hz, 2H, H2′, H6′), 7.30 (d, J = 8.5 Hz, 2H, H5′, H3′), 2,9 (m, 1H, $HC(CH_3)_2$),1.28 (d, J = 6.8 Hz, H_3CCH), 1.27 (d, J = 7.2 Hz, H_3CCH); EIMS m/z 322 (M^+, 6), 161 (i-Pr-C_6H_4C═NO, 34), 120 (i-PrC_6H_4 + H, 100).

5-(Chloromethyl)-3-phenyl-4,5-dihydro-1,2-oxazole (6a). It was obtained as a brownish wax. IR (KBr) ν: 2940, 2924, 2854, 1597, 1560, 1490, 1445, 1375, 1355, 1266, 1073, 1000, 911, 892, 812, 762, 739, 692, 546 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.68 (m, 2H, H2′, H6′), 7.42 (m, 3H, H5′, H4′, H3′), 4.99 (m, 1H, H5), 3.72 (dd, J = 11.3; 4.3 Hz, 1H, H6a), 3.58 (dd, J = 11.3; 7.5 Hz, 1H, H6b), 3.50 (dd, J = 16.9; 10.5 Hz, 1H, H4a), 3.35 (dd, J = 16.9; 6.4 Hz, 1H, H4b); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.1 (C3), 130.3 (C1′), 129.0 (C4′), 128.7 (C6′, C2′), 126.7 (C3′, C5′), 79.7 (C5), 44.8 (C4), 38.5 (C6); ^{15}N NMR (600 MHz, $CDCl_3$, from HMBC) δ: −15.5 (N-2) (H4a, H4b); EIMS m/z 195 (M^+), 197 (M^+). HRMS Calcd for $C_{10}H_{10}ClNO$ = 195.0451, found 195.0424.

5-(Chloromethyl)-3-[4-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole (6b). It was obtained as a white solid, mp 82–83°C. IR (KBr) ν: 2920, 2850, 1616, 1598, 1562, 1440, 1412, 1328, 1242, 1169, 1111, 1070, 1035, 1014, 970, 916, 890, 873, 845, 820, 760, 727, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.88 (d, J = 8.5 Hz, 2H, H5′, H3′), 7.67 (d, J = 8.5 Hz, 2H, H6′, H2′), 5.06 (m, 1H, H5), 3.75 (dd, J = 11.5; 4.0 Hz, 1H, H6a), 3.62 (dd, J = 11.5; 7.5 Hz, 1H, H6b), 3.52 (dd, J = 17.0; 10.5 Hz, 1H, H4a), 3.37 (dd, J = 17.0; 6.8 Hz, 1H, H4b); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 155.4 (C3), 132.7 (C1′), 127.8 (q, J = 18.5 Hz, C4′), 127.2 (C6′, C2′, 2C), 126.0 (q, J = 4.0 Hz, 2C, C3′, C5′), 80.5 (C5), 44.9 (C4), 38.3 (C6); ^{19}F NMR (471 MHz, $CDCl_3$) δ: −63.3; EIMS m/z 263 (M^+, 40), 244 ($M^+ - F$, 10), 214 ($M^+ - CH_2Cl$, 86), 186 ($M^+ - CH_2Cl - C_2H_4$, 100); HRMS Calcd for $C_{11}H_9NOClF_3$ 263.0325, found 263.0316.

5-Methyl-3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1,2-oxazole (7). It was obtained as an oil in 2–10% yield. IR (KBr) ν: 2925, 2854, 1619, 1598, 1562, 1490, 1457, 1432, 1411, 1380, 1330, 1169, 1129, 1073, 1034, 970, 918, 909, 848, 838, 810, 770, 740, 601 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz) δ: 7.91 (d, J = 8.2 Hz, 2H, H5′, H3′), 7.78 (d, J = 8.2 Hz, 2H, H6′, H2′), 4.91 (m, 1H, H5), 3.58 (dd, J = 16.7; 10.3 Hz, 1H, H4a), 3.07 (dd, J = 16.7; 8.3 Hz, 1H, H4b), 1.39 (d, J = 6.3 Hz, 3H, H_3C); ^{13}C NMR (151 MHz, acetone-d_6, from HMBC) δ: 156.3 (C3) (H2′, H6′, H4a, H4b), 135.2 (C4′) (H5′, H3′), 131.4 (C1′) (H2′, H6′), 127.9 (C6′, C2′) (H3′, H5′, H2′, H6′), 126.4 (C3′, C5′) (H6′, H2′, H5′, H3′), 124.2 (CF_3) (H3′, H6′), 79.0 (C5) (H4a, H4b, H_3C), 41.4 (C4) (H_3C), 21.1 (CH_3) (H4a, H4b); ^{19}F NMR (471 MHz, $CDCl_3$) δ: −63.25; ^{15}N NMR (600 MHz, acetone-d_6, HMBC) δ: −6.7 (N2) (H4a, H4b); ESI-MS m/z 252 (M^+ + Na), 230 (M^+ + H); HRMS: Calcd for $C_{11}H_{11}NOF_3$ 230.0793, found 230.0802.

***3-[(4-(Trifluoromethyl)phenyl]-N*-(4-methoxyphenyl)-6-methyl-7a-[4-(trifluoromethyl)phenyl]-7,7a-dihydro-6*H*-[1,2]oxazolo[2,3-*d*][1,2,4]oxadiazole-7-carboxamide (8)**. It was obtained in 7% yield as a wax. IR (KBr) ν: 2940, 2927, 2840, 1666, 1620, 1601, 1513, 1460, 1413, 1325, 1300, 1245, 1170, 1131, 1068, 1020, 910, 860, 840, 801, 780, 700, 678, 605 cm^{-1}. ^{1}H NMR (acetone-d_6, 600 MHz) δ: 8.98 (s, 1H, NH), 8.16 (d, J = 8.1 Hz, 2H, H2″, H6″), 7.97 (d, J = 8.3 Hz, 2H, H3′, H5′), 7.90 (d, J = 8.1 Hz, 2H, H3″, H5″), 7.86 (d, J = 8.3 Hz, 2H, H2′, H6′), 7.49 (dd, J = 9.1; 2.8 Hz, 2H, H2‴, H6‴), 6.89 (dd, J = 9.1; 2.8 Hz, 2H, H3‴, H5‴), 4.62 (dq, J = 10.4; 5.9 Hz, 1H, H6), 3.77 (s, 3H, H_3CO), 3.60 (d, J = 10.4 Hz, 1H, H7), 1.38 (d, J = 5.9 Hz, 3H, H_3C); ^{13}C NMR (acetone-d_6, 125 MHz, from HMBC) δ: 161.9 (C═O), 157.4 (C3), 156.5 (C4‴), 143.1 (C1′), 132.8 (C1″), 132.1 (C1‴), 131.5 (C4′), 128.7 (CF_3″), 128.2 (C2″, C6″), 127.3 (CF_3′), 126.7 (C2′, C6′), 126.2 (C3″, C5″), 125.7 (C3′, C5′), 125.0 (C4″), 121.5 (C2‴, C6‴), 113.7 (C3‴, C5‴), 107.8 (C7a), 78.7 (C6), 69.0 (C7), 54.0 (CH_3O), 14.7 (CH_3); ^{19}F NMR (acetone-d_6, 470 MHz) δ: −63.6, −63.1; ^{15}N NMR (600 MHz, acetone-d_6, from HMBC) δ: −247.5 (HNC═O, J_{15N-1H} = 100 Hz) (HN, H2‴, H6‴), −66.2; FD-MS m/z 565 (M^+, 27), 531 (34), 358 (74), 207(60), 173 (58); HRMS: Calcd for $C_{27}H_{21}N_3O_4F_6Na$ 588.1334, found 588.1346.

***N*-(4-Methoxyphenyl)-7-oxo-3a-[4-(trifluoromethyl)phenyl] tetrahydro-2*H*,5*H*-[1,2]oxazolo[3,2-*b*][1,3]oxazine-2-carboxamide (10)**. It was obtained as a white down, mp 186–187°C (dichloromethane-hexanes), 25%. The yield was increased to 65%, when a threefold excess of the dipolarophile was applied. IR (KBr) ν: 3377, 3150, 3120, 3020, 2990, 2930, 2840, 1749 (δ-lactam), 1668 (O═CNH, amide), 1630, 1600, 1530, 1514, 1453, 1412, 1324, 1300, 1260, 1240, 1200, 1170, 1128, 1105, 1070, 1035, 901, 831, 805, 770, 760, 650 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz) δ: 9.09 (s, 1H, NH), 7.86 (d, J = 8.2 Hz, 2H, H2′, H6′), 7.75 (d, J = 8.2 Hz, 2H, H3′, H5′), 7.52 (dt, J = 7.6; 2.1 Hz, 2H, H2″, H6″), 6.83 (dt, J = 7.6; 2.1 Hz, 2H, H3″, H5″), 5.29 (dd, J = 11.8; 6.7 Hz, 1H, H2), 4.50 (m, 2H, H5), 3.81

(dd, $J = 17.2$; 11.8 Hz, 1H, $H3_x$), 3.73 (s, 3H, H_3CO), 3.71 (dd, $J = 17.2$; 6.7 Hz, 1H, $H3_y$), 2.73 (t, $J = 6.2$ Hz, 2H, H6); ^{1}H NMR (CD_2Cl_2, 600 MHz) δ: 7.74 (d, $J = 8.2$ Hz, 2H, H2′, H6′), 7.65 (d, $J = 8.2$ Hz, 2H, H3′, H5′), 7.38 (dt, $J = 9.0$ Hz, 2H, H2″, H6″), 7.24 (bs, 1H, NH), 6.83 (dt, $J = 9.0$; 1.9 Hz, 2H, H3″, H5″), 5.23 (dd, $J = 10.3$; 8.1 Hz, 1H, H2), 4.55 (t, $J = 6.1$ Hz, 2H, H5), 3.78 (s, 3H, OCH_3), 3.65 (d, $J = 8.1$ Hz, 1H, H3A), 3.64 (d, $J = 10.3$ Hz, 1H, H3B), 2.71 (t, $J = 6.1$ Hz, 2H, H6) ppm; ^{19}F NMR (470 MHz, acetone-d_6) $\delta = -63.4$; EIMS *m/z* (% intensity) 436 (M^+, 19), 265 (10), 177 (27, $H_2C{=}CHCONHC_6H_4OCH_3$), 172 (25), 145 (15, $F_3CC_6H_4$), 125 (100, $H{=}NC_6H_4OCH_3$); ESI-MS *m/z* 459 ($M^+ + Na$); HR ESI-MS: Calcd for $C_{21}H_{19}F_3N_2O_5Na = 459.1144$, found 459.1149. *Anal*. Calcd for $C_{21}H_{19}F_3N_2O_5$: C, 57.80; H, 4.39; N, 6.42. Found: C, 57.78; H 4.41; N, 6.35.

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