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1,3-DIPOLAR CYCLOADDITION REACTIONS OF BENZONITRILE OXIDE TO 2(1*H*)-PYRAZINONE AND ITS *N*- AND *O*-METHYL DERIVATIVES

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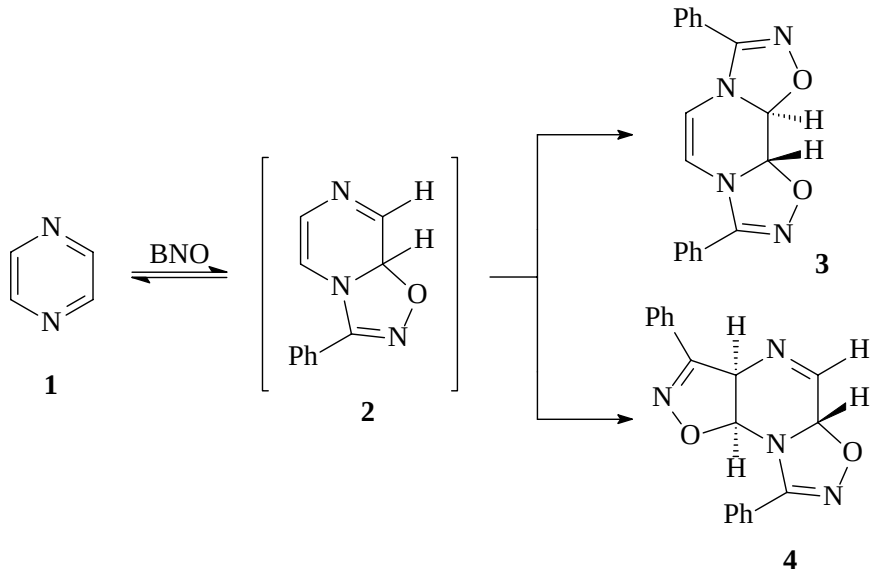
Abstract - 2(1*H*)-Pyrazinone, which is in equilibrium with 2-pyrazinol, reacts with benzonitrile oxide (BNO) affording the N_1-adduct with a 67% yield, while 2-methoxypyrazine gives two methoxypyrazinones (*ca*. 3%) and a biscycloadduct together with its degradation product, which derive from the two unisolable monocycloadducts to the $C=N_4$ double bond. *N*-Methylpyrazinone gives only the degradation product (3.4%) of the initial monocycloadduct of BNO to $C=N_4$ double bond.

Recently, we investigated the reactions of benzonitrile oxide (BNO) with aromatic diazines[1] within a study aimed at analysing the effect of the aza-substitution on the reactivity, regio- and stereochemistry of pyridine nucleus, the dipolarophilic reactivity of which has been object of previous researches by us[2-4] and others.[5-8]

Among the three diazines, we found that pyrazine (**1**) behaves like pyridine affording an unisolable intermediate monocycloadduct (**2**), deriving from the addition of BNO in a concerted pseudopericyclic cycloaddition,[9] which in its turn originates the two stable cycloadducts (**3**) and (**4**), where a second molecule of BNO is regio- and *anti*-stereospecifically added to the C=N or C=C double bond of **2** (Scheme 1). The aza-substitution in the γ-position of the dienaminic system of monocycloadduct (**2**) increases the reactivity of the γ,δ-double bond and reverses the regiochemistry of the γ,δ-attack with respect to pyridine,[2] too.



Scheme 1

As extension of this line of research we have investigated the reactivity of 2(1*H*)-pyrazinone (**5A**) which is in equilibrium with 2-pyrazinol (**5B**) and their *N*- (**6**) and *O*-methyl derivatives (**7**) towards BNO. The study of these reactions appeared to us very interesting because they represent an unexplored route to the synthesis of dihydroisoxazolo- or isoxazolo[4,5-*b*]pyrazine nucleosides which are analogous of the naturally occurring purine nucleosides. In old works the construction of such heterocycles was carried out starting from the rather unstable 4,5-diaminoisoxazole isolated as hydrochloride.[10-12]

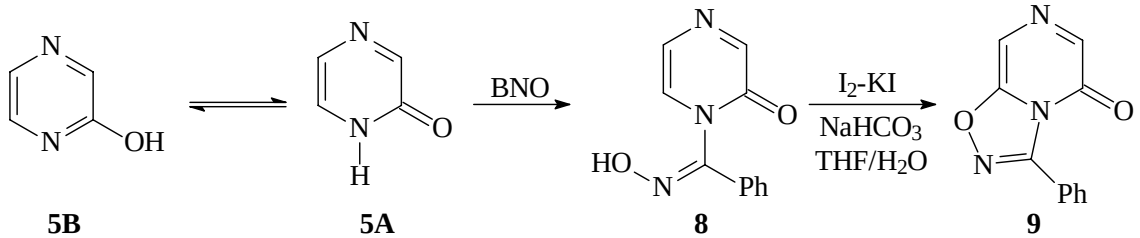
To our best knowledge, the dipolarophilic reactivity of 2-pyrazinone (**5**) and its *N*- (**6**) and *O*-methyl derivatives (**7**) has been neglected. Only 2,5- and 2,6-dihydroxypyrazines participate in a number of interesting cycloaddition reactions, but as 1,3-dipoles.[13-15]

RESULTS AND DISCUSSION

Reactions were conducted by slowly adding three equivalents of a triethylamine solution in methanol to a stirred, ice cooled, solution of pyrazine derivatives (**5-7**) and benzhydroximic acid chloride in the 1:3 ratio in the same solvent. After heating to room temperature, the reaction mixture was allowed under stirring for two days and then the solvent was removed and the residue was chromatographed. When ether, chloroform or benzene were used as solvents, reaction mixtures afforded slightly different yields of the same products and in some cases only a new *N*-addition product was isolated. Because of their insolubility in the latter solvents, reactions of **5** and **6** were conducted in suspension and in these cases the separated solid was filtered and then analyzed, while the filtrate was treated as above.

2(1H)-Pyrazinone

From literature data[16-21] evidence exists that 2(1*H*)-pyrazinone (**5A**) is in equilibrium with 2-hydroxypyrazine (**5B**), where the first is the dominant tautomer. We found that only **5A** reacts with BNO in methanol affording the N_1-adduct (**8**) with a 67.6% yield, but **5B** is probably involved in the addition of BNO to the N_1-nitrogen of **5**. The presence of the hydroxy group in the 2-position favours the formation of a hydrogen bonding with the oxygen of the 1,3-dipole and then the attack of the N_1-nitrogen of **5** to the carbon of the 1,3-dipole.



5B **5A** **8** **9**

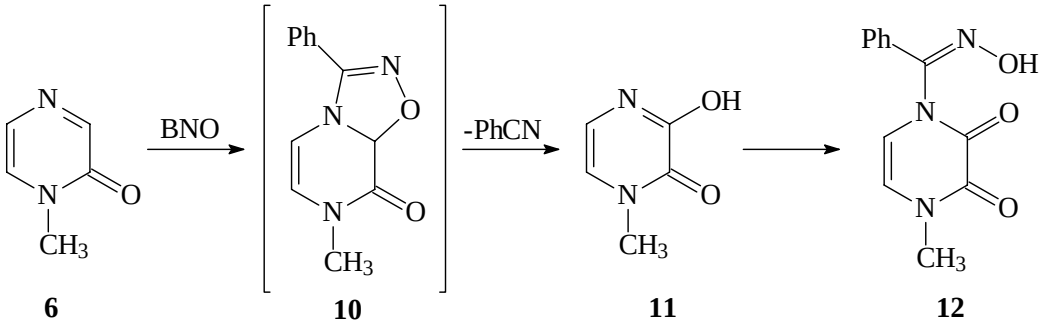
Scheme 2

The structure of **8** was inferred from spectral and chemical data. Its IR spectrum shows two absorptions at 3447 br and 1675 cm^{-1}; in its ^{1}H-NMR spectrum signals of pyrazinone H_5- and H_6-protons are covered by those of phenyl ring, while those of the H_3 pyrazinone and amidoxime protons appear at 8.21 and 12.32 ppm; besides signals of carbons of phenyl group, its ^{13}C-NMR spectrum contains signals at 130.31, 130.39, 144.26 and 153.03 ppm for C_5-, C_6-, C_3- and C_2-pyrazine carbons and at 150.51 ppm for amidoxime carbon. By oxidation with iodine-potassium iodide in aqueous tetrahydrofuran in the presence of sodium bicarbonate,[22] **8** afforded 3-phenyl-5*H*-[1,2,4]oxadiazolo[4,5-*a*]pyrazin-5-one (**9**), whose IR and ^{1}H-NMR spectra do not show the absorption of the hydroxy group and ^{13}C-NMR spectrum exhibits another quaternary carbon at 158.92 ppm.

1-Methyl-2(1H)-pyrazinone

1-Methyl-2(1*H*)-pyrazinone (**6**) is a very poor dipolarophile because of the deactivating effect of the carbonyl and methylamino groups on the cyclic system. It reacts with BNO in methanol giving only a 3.4% yield of 1-methyl-3-hydroxypyrazin-2-one (**11**) deriving from the unisolable monocycloadduct (**10**) of BNO to the $C{=}N_4$ double bond of **6**, which remains the most reactive site of the molecule. Monocycloadduct (**10**) then undergoes the degradation process with the loss of benzonitrile because of the autoxidation (Scheme 3).[2, 3]

^{1}H- and ^{13}C-NMR spectra of **11** support the assigned structure because, besides the signal of methyl protons and carbon at 3.41 and 38.31 ppm, respectively, the ^{1}H-NMR spectrum shows two doublets at 6.18 and 6.47 ppm for pyrazinone H_6- and H_5-protons and a broad singlet at 11.35 ppm for the hydroxy proton, while the ^{13}C-NMR shows signals at 119.59 and 129.14 ppm for olefinic C_6- and C_5-carbons and at 154.40 and 155.72 ppm for carbonyl carbons. Furthermore the IR spectrum contains absorption bands at 3260 br and 1670 cm^{-1} for hydroxy and carbonyl groups, respectively.



6 **10** **11** **12**

Scheme 3

Pyrazinedione (**11**) separates together with triethylamine hydrochloride as a precipitate when the reaction is carried out in ether or benzene suspension with a yield of 2.8 and 1.9%, respectively. When chloroform was used as a solvent, the chromatography eluted also another compound (**12**) (2.8% yield) which derives

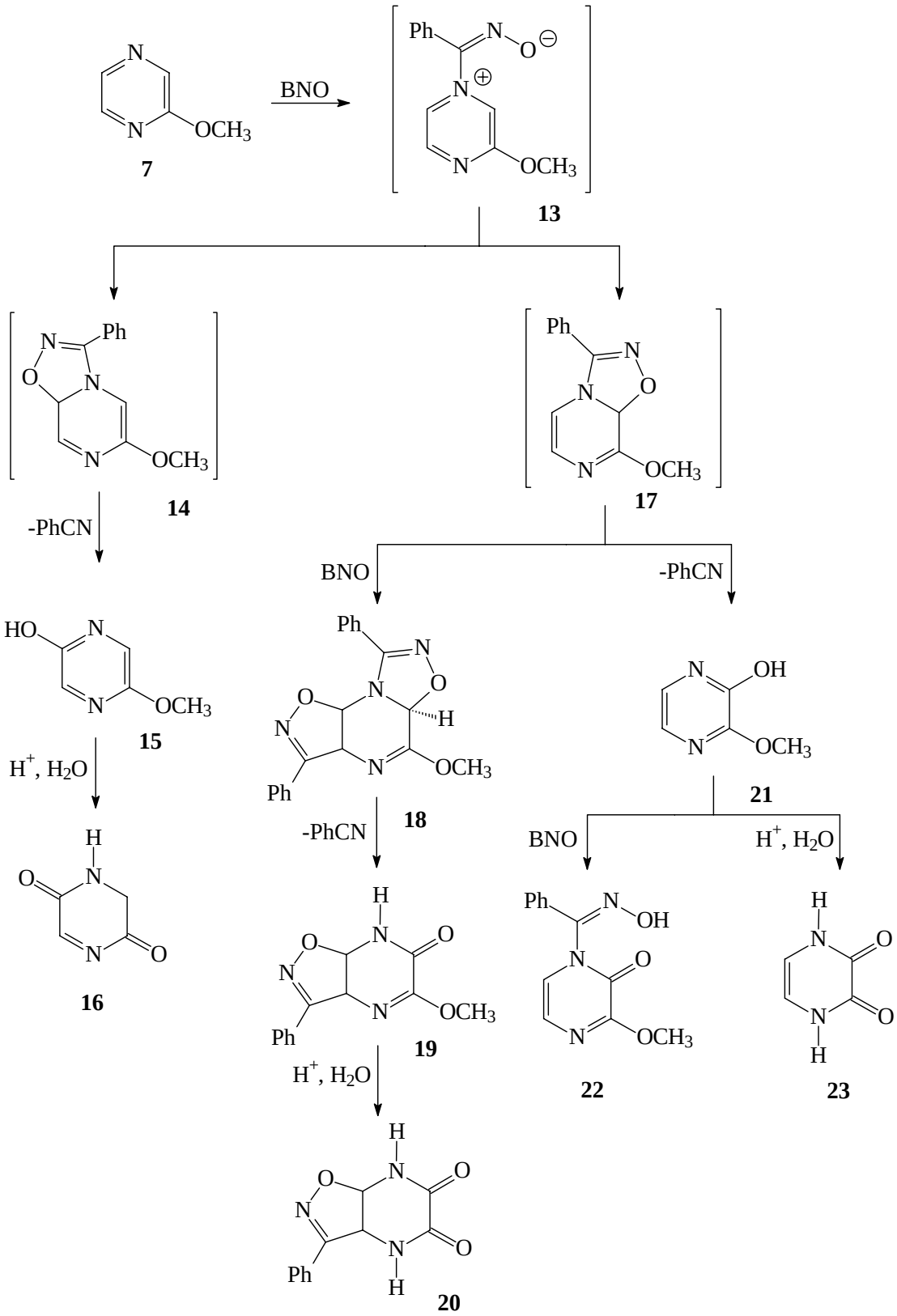
from the addition of BNO to the N_4-nitrogen of **11**, this latter isolated with a 2.5% yield. Besides signals relative to phenyl protons and carbons, the ^{1}H-NMR spectrum contains an oxime proton at 12.45 ppm and ^{13}C-NMR spectrum contains another signal of quaternary carbon at 158.18 ppm; the IR spectrum shows the broad band of hydroxy group at 3398 cm^{-1}.

2-Methoxypyrazine

The reaction mixture of 2-methoxypyrazine (**7**) with BNO in ether afforded the two methoxypyrazinones (**15**) (3.0%) and (**21**) (2.8%) and a biscycloadduct (**18**) (9.6%), which latter derives from the addition of a second molecule of BNO to the C=C double bond of **17**, together with its degradation product (**19**) (6.2%) (Scheme 4). As separately it was proven, the biscycloadduct (**18**) degrades into **19** and benzonitrile upon standing in different solvents. Pyrazinones (**15**) and (**21**) are originated from monocycloadducts (**14**) and (**17**) which are unstable to the autoxidation process leading to the loss of benzonitrile[2,3] in the reaction conditions. They have been well distinguished because in the ^{1}H-NMR spectra the signals of H_3- and H_6-protons of **15** appear as singlets at 8.14 and 7.97 ppm and those of H_5- and H_6-protons of **21** appear as doublets at 6.94 and 7.00 ppm, respectively; in the ^{13}C-NMR spectra signals of C_3- and C_6-carbons of **15** are at 142.36 and 140.60 ppm, while those of C_5- and C_6-carbons of **21** are at 112.36 and 119.72 ppm.

In an attempt of acid hydrolysis by 20% hydrochloric acid methoxypyrazinones (**15)** and (**21)** afforded the known pyrazinones (**16**)[23] and (**23**).[24]

When the reaction mixture was conducted in methanol compound (**22**) was also isolated. It derives from the addition of BNO to the N_1-nitrogen of **21** and the structure of which has been inferred from spectral data. Its IR spectrum is characterized by absorptions at 3430 br and 1660 cm^{-1} which are attributable to the oximic hydroxy and carbonyl groups, respectively. Its ^{1}H-NMR spectrum contains two doublets at 6.94 and 7.10 ppm for H_5- and H_6-protons and a broad singlet at 12.25 ppm for the oximic proton, while its ^{13}C-NMR spectrum contains the signal of another quaternary carbon at 156.57 ppm. Also structures of **18** and **19** rely upon their spectroscopic data and upon acid hydrolysis of **19**, which afforded dihydroisoxazole[4,5-*b*]-1,4-dihydropyrazine-2,3-dione (**20**). The ^{1}H-NMR spectrum of **18** shows a singlet at 5.73 ppm for the H_5-oxadiazole proton and two doublets at 5.29 and 5.74 ppm with J = 8.2 Hz for H_4- and H_5-isoxazole protons, besides the signal of methoxy proton at 3.78 ppm. The ^{13}C-NMR spectrum shows signals relative to the methoxy carbon at 53.71 ppm, the isoxazoline ring carbons at 60.63, 79.80 and 156.00 ppm and the oxadiazoline ring carbons at 81.72 and 150.00 ppm. The *anti*-stereochemistry of **18** could not be deduced from its spectra, but it is proposed by analogy to pyridine,[4] pyrimidine[8] and pyridazine[8] biscycloadducts, whose stereochemistry relies upon an X-Ray crystallographic analysis.

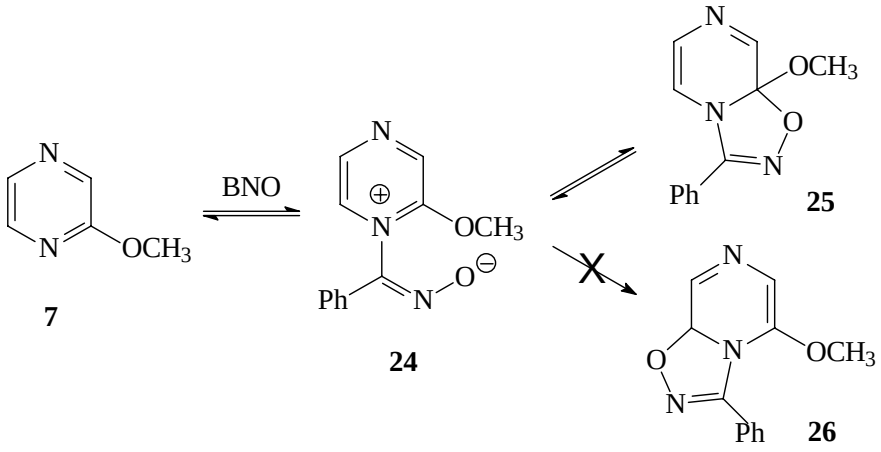

BNO
7
13
14
17
-PhCN
BNO
-PhCN
15
18
21
H+, H2O
-PhCN
BNO
H+, H2O
16
19
22
23
H+, H2O
20

Scheme 4

Besides the broad signal at 7.33 ppm relative to the amide proton, the ^{1}H-NMR spectrum of **19** contains signals of methoxy and H_4- and H_5-isoxazoline protons at 3.76, 5.45 and 5.93 ppm. This latter appears as double doublet[25] and confirms the assigned regiochemistry. Its ^{13}C-NMR spectrum contains another quaternary carbon at 152.80 ppm and its IR spectrum shows an absorption at 1660 cm^{-1}. The disappearance of the signal relative to the methoxy protons and carbon in their ^{1}H- and ^{13}C-NMR spectra and the appearance of another carbonyl carbon at 156.15 ppm characterize the ^{13}C-NMR spectrum of **20**.

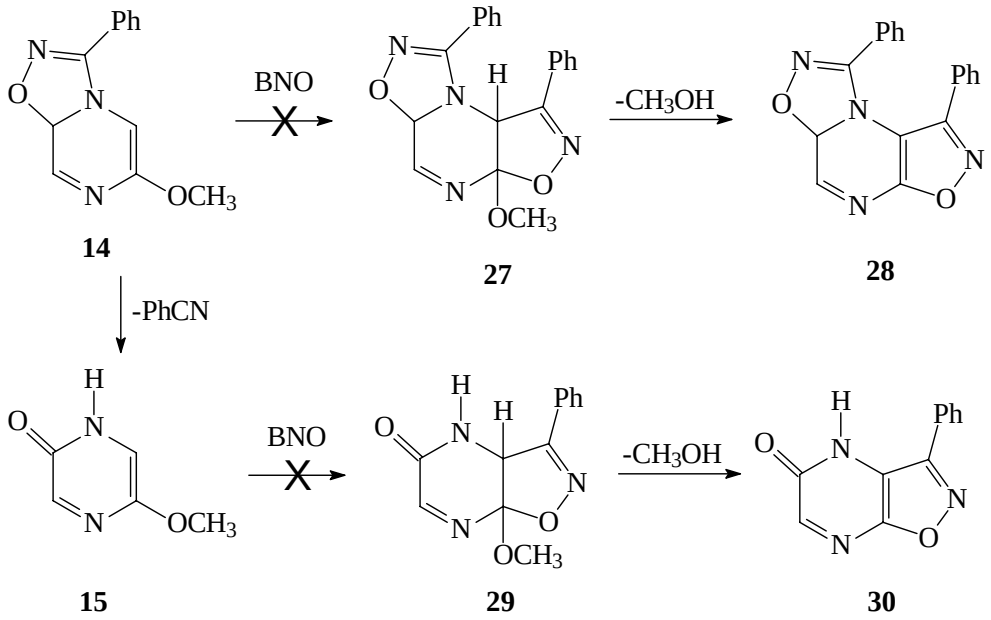
These results are in line with our previous mechanistic hypothesis on the reactivity of pyridine towards BNO,[2] which involves a mechanism of pesudopericyclic reaction.[9] Monocycloadducts (**14**) and (**17**) are viewed as secondary products which derive from the electrocyclic closure of the initial adduct **13** of BNO to the N_4-nitrogen of **7**. The oxygen atom of the dipole then cyclizes on the C_3- or C_5-carbons affording the two corresponding unstable monocycloadducts, which undergo either the autoxidation process[2,3] or the addition of second molecule of BNO to the C=C double bond of **7** to give the biscycloadduct (**18**).

In contrast with the reaction of BNO with **5**, where the presence of the hydroxy group in the 2-position directs the attack to the N_1-nitrogen to the 1,3-dipole carbon, in this case of **7** only the N_4-nitrogen is reactive towards BNO because of the presence of the methoxy group which is unfavourable to the attack of BNO to the N_1-nitrogen to give the zwitterion (**24**) (Scheme 5). Indeed, the electrocyclization of **24** on the C_2-carbon would lead to the reversible formation of the ketal (**25**), while that one on C_6-carbon to give **26** does not take place because of the steric hindrance of the 1,3-dipole phenyl ring with the methoxy group.



Scheme 5

We have searched for one of our target reaction products (**28**) or (**30**), which should be obtained by elimination of methanol from cycloadducts (**27**) or (**29**)**,** but without success (Scheme 6). Probably these latter, which are also favoured by the electron donor effect of methoxy group, as well as other conceivable products are formed in our reaction conditions, but their yields are so low that they escape their isolation from the reaction mixture.



Scheme 6

In conclusion, the results of these reactions examined by us show that only the route for dihydroisoxazolopyrazine heterocycles through a 1,3-dipolar cycloaddition process of **7** with BNO, followed by an acid hydrolysis can be useful, even if the yield remains modest.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. ^{1}H-NMR spectra were recorded on a Varian 200 spectrometer using tetramethylsilane as internal standard and deuterochloroform or DMSO-d_6 as solvents. IR spectra were recorded on a Perkin Elmer Paragon 500 FT IR spectrophotometer using potassium bromide discs and MS on a VG ZAB-2SE spectrometer operating at 70 eV. Thin layer chromatography were performed on aluminium plates pre-coated with Merck silica gel 60-F_{254}. Preparative chromatographic separations of reaction mixtures were performed by means of gravity or flash chromatography using Merck silica gel 60 and in some cases by means of centrifugally enhanced preparative thin layer chromatography using Merck silica gel 60 PF_{254}. Mixtures of cyclohexane-ethyl acetate were used as eluents.

Starting materials.

Benzhydroximic acid chloride was obtained by treatment of benzaldoxime with sodium hypochlorite;[26] 2(1*H*)-pyrazinone,[27] 1-methyl-2(1*H*)-pyrazinone[28] and 2-methoxypyrazine[27] were prepared from 2-chloropyrazine following literature procedures. Benzaldoxime and 2-chloropyrazine are commercial

compounds and have been purchased from the Aldrich Co. Eluents used in chromatography were reagent grade. Solvents were dried following literature procedures.[29]
The identification of samples deriving from different experiments was secured by mixed melting points and IR spectra.

*General procedure for reactions of BNO with pyrazine derivatives (**5**-**7**).*
To a stirred, ice cooled, solution of benzhydroximic acid chloride (0.3 mol) and pyrazine derivative (0.1 mol) in anhydrous methanol (100 mL) 0.3 mol of triethylamine in the same solvent (30 mL) were added over a period of 0.5 h. After having warmed the reaction mixture to rt, it was allowed under stirring for two days and then the solvent was removed and the residue was chromatographed. The same reactions were repeated in solution or suspension because of the insolubility of pyrazinones, in ether, benzene and chloroform. In these cases a solid separated which was filtered and then analysed, while the filtrate was worked up as above.

1-[(Hydroxyimino)(phenyl)methyl]pyrazin-2(1H)-one (**8**): 67.6% yield, mp 190-191 °C, pale yellow crystals from ethyl acetate (*Anal*. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.42; H, 4.19; N, 19.49); ν_{max} (KBr): 3447 br, 1675 cm^{-1}; δ_H (DMSO-d_6): 7.43-7.56 (7H, m, phenyl H, pyrazinone H_5 and H_6), 8.21 (1H, s, pyrazinone H_3), 12.32 (1H, br s, hydroxy H); δ_C (DMSO-d_6): 123.09, 125.46, 128.79, 128.88, 128.92, 128.96 (phenyl C), 130.31(pyrazinone C_6), 130.39 (pyrazinone C_5), 144.26 (pyrazinone C_3), 152.51 (pyrazinone C_2), 155.03 (amidoxime C); MS: m/z 215 (M^+).

*Conversion of **8** into **9** by iodine-potassium iodide oxidation.*
To a stirred solution of **8** (430 mg, 2 mmol) in tetrahydrofuran (40 mL) was added a solution of sodium bicarbonate (680 mg, 8.1 mmol) in water (50 mL). The reaction mixture was protected from light, and a solution of potassium iodide (1,175 g, 7.0 mmol) and iodine (541 mg, 2.1 mmol) in water (100 mL) was added to it. After refluxing for 4 h, the mixture was diluted with concentrated sodium bisulfide solution (150 mL), extracted with ether, dried over sodium sulfate and then evaporated at reduced pressure. The crystallization of the residue gave 350 mg of *3-phenyl-5H-[1,2,4]oxadiazolo[4,5-a]pyrazin-5-one* (**9**): 85.1% yield, mp 152-154 °C, colourless crystals from ethanol (*Anal*. Calcd for $C_{11}H_7N_3O_2$: C, 62.00; H, 3.28; N, 19.75. Found: C, 61.97; H, 3.31; N, 19.71); ν_{max} (KBr): 1672 cm^{-1}; δ_H ($CDCl_3$): 7.15 (1H, s, pyrazinone H-3) 7.48-7.52 (3H, m, phenyl H), 7.59-7.62 (2H, m, phenyl H), 8.12 (1H, s, pyrazinone H-5); δ_C ($CDCl_3$): 122.40, 130.90, 131.06, 131.43, (phenyl C), 134.60 (pyrazinone C-3), 150.92 (pyrazinone C-5), 152.36 (pyrazinone C-6), 154.21 (oxadiazole C-3), 158.92 (oxadiazole C-5); MS: m/z 213 (M^+).

1-Methyl-3-hydroxypyrazine-2-one (**11**): 3.4% yield, mp 229-231 °C (lit.,[30] mp 230-232 °C) colourless crystals from ethanol (*Anal*. Calcd for $C_5H_6N_2O_2$: C, 47.6; H, 4.8; N, 21.20. Found: C, 47.9; H, 5.1; N, 22.0); ν_{max} (KBr): 1692, 1670 cm^{-1}; δ_H (DMSO-d_6): 3.40 (3H, s, methyl H), 6.18 (1H, d, *J* = 5.2 Hz, pyrazine H-6), 6.40 (1H, d, *J* = 5.2 Hz, pyrazine H-5), 11.35 (1H, br s, hydroxy H); δ_C (DMSO-d_6): 38.31 (methyl C), 119.78 (pyrazine C-5), 129.27 (pyrazine C-6), 154.40 (pyrazine C-3), 155.72 (pyrazine C-2); MS: m/z 126 (M^+).

1-[(Hydroxyimino)(phenyl)methyl]-4-methyl-1,4-dihydropyrazine-2,3-dione (**12**): 2.8% yield, mp 189-191 °C, colourless crystals from ethyl acetate (*Anal*. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.84; H, 4.55; N, 17.18); ν_{max} (KBr): 3496 br, 1672 cm^{-1}; δ_H (DMSO-d_6): 3.59 (3H, s, methyl H), 6.53 (1H, d, *J* = 5.8 Hz, pyrazine H-6), 6.80 (1H, d, *J* = 5.8 Hz, pyrazine H-5), 7.58-7.64 (3H, m, phenyl H), 7.80-7.88 (2H, m, phenyl H), 12.41 (1H, br s, hydroxy H); δ_C (DMSO-d_6): 37.18 (methyl C), 113.13 (pyrazine C-5), 116.54 (pyrazine C-6), 128.02, 130.80, 132.21, 139.82 (phenyl C), 150.75 (pyrazine C-3), 153.80 (pyrazine C-2), 158.18 (amidoxime C); MS: m/z 245 (M^+).

2-Hydroxy-5-methoxypyrazine (**15**): 3.0% yield, mp 168-170 °C, colourless crystals from ethanol (*Anal*. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.59; H, 4.82; N, 22.19); ν_{max} (KBr): 3258 br cm^{-1}; δ_H (DMSO-d_6): 3.98 (3H, s, methoxy H), 7.97 (1H, s, pyrazine H-6), 8.14 (1H, s, pyrazine H-3), 11.23 (1H, br s, hydroxy H); δ_C (DMSO-d_6): 54.90 (methoxy C), 140.60 (pyrazine C-6), 142.36 (pyrazine C-3), 148.50 (pyrazine C-5), 153.23 (pyrazine C-2); MS: m/z 126 (M^+).

5-Methoxy-3,8-diphenyl-3a,9a-dihydro-5aH-isoxazolo[4',5':5,6]pyrazino[1,2-d][1,2,4]oxadiazole (**18**): 9.6% yield, mp 174-176 °C, pale yellow crystals from ethyl acetate (*Anal*. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.57; H, 4.58; N, 16.18); ν_{max} (KBr): 1600, 1570, cm^{-1}; δ_H ($CDCl_3$): 3.78 (3H, s, methoxy H), 5.29 (1H, d, *J* = 8.2 Hz, dihydroisoxazole H-4), 5.73 (1H, s, dihydroxadiazole H-5), 5.74 (1H, d, *J* = 8.2 Hz, dihydroisoxazole H-5), 7.41-7.97 (10H, m, phenyl H); δ_C ($CDCl_3$): 53.71 (methoxy C), 60.63 (dihydroisoxazole C-5), 79.80 (dihydroisoxazole C-4), 81.72 (dihydroxadiazole C-5), 127.29, 128.17, 128.63, 129.34, 130.60,131.90, 132.11, 140.32 (phenyl C), 156.00 (dihydroisoxazole C-3), 158.38 (dihydroxadiazole C-3), 159.69 (pyrazine C-2); MS: m/z 348 (M^+).

5-Methoxy-3-phenyl-7,7a-dihydroisoxazolo[4,5-b]pyrazin-6(3aH)-one (**19**): 6.2% yield, mp 196-198 °C, pale yellow crystals from ethyl acetate (*Anal*. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.87; H, 4.58; N, 17.18); ν_{max} (KBr): 1660 cm^{-1}; δ_H ($CDCl_3$): 3.76 (3H, s, methoxy H), 5.45 (1H, d, *J* = 7.8 Hz, dihydroisoxazole H-4), 5.83 (1H, dd, J_1 = 7.8 Hz, J_2 = 4.2 Hz, dihydroisoxazole H-5), 7.33 (1H,

br s, amide H), 7.93-7.98 (5H, m, phenyl H); δ_C ($CDCl_3$): 54.26 (methoxy C), 62.41 (dihydroisoxazole C-4), 84.16 (dihydroisoxazole C-5), 127.35, 127.63, 128.01, 128.80, 130.75 (phenyl C), 152.25 (pyrazine C-3), 152.80 (dihydroisoxazole C-3), 157.63 (pyrazine C-2); MS: m/z 245 (M^+).

2-Hydroxy-3-methoxypyrazine (**21**): 2.8% yield, mp 201-203 °C (lit.,[31] mp 205 °C), colourless crystals from ethanol (*Anal*. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.67; H, 4.88; N, 22.18); ν_{max} (KBr): 3420 br cm^{-1}; δ_H (DMSO-d_6): 4.01 (3H, s, methoxy H), 6.91 (1H, d, *J* = 4.2 Hz, pyrazine H-6), 7.00 (1H, d, *J* = 4.2 Hz, pyrazine H-5), 12.64 (1H, br s, hydroxy H); δ_C (DMSO-d_6): 53.50 (methoxy C), 112.36 (pyrazine C-5), 119.72 (pyrazine C-6), 152.54 (pyrazine C-2), 158.28 (pyrazine C-3); MS: m/z 126 (M^+).

1-[(Hydroxyimino)(phenyl)methyl]-3-methoxypyrazin-2(1H)-one (**22**): 2.1% yield, mp 190-192 °C, colourless crystals from ethanol (*Anal*. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.87; H, 4.48; N, 17.21); ν_{max} (KBr): 3430 br, 1660 cm^{-1}; δ_H (DMSO-d_6): 3.88 (3H, s, methoxy), 6.94 (1H, d, *J* = 4.5 Hz, pyrazine H-5), 7.09 (1H, d, *J* = 4.5 Hz, pyrazine H-6), 7.43-7.52 (5H, m, phenyl H), 12.25 (1H, s, hydroxy H); δ_C (DMSO-d_6): 54.10 (methoxy C), 118.57, 122.10, 125.43 (phenyl C), 130.23 (pyrazine C-5), 130.40 (pyrazine C-6), 154.24 (pyrazine C-2), 158.34 (pyrazine C-3), 156.57 (amidoxime C); MS: m/z 245 (M^+).

Acid hydrolysis of adducts (**15**, **19** *and* **21**).

A solution of **15**, **19** or **21** (4 mmol) in ethanol (10 mL) containing 20% hydrochloric acid (2 mL) was refluxed for 6 h. After cooling the mixture was poured on ice and extracted with chloroform. The combined extracts were washed with 5% sodium hydroxide and dried on anhydrous sodium sulphate. The solvent was evaporated to give products (**16**),[23] (**20**) or (**23**),[24] of which **16** and **23** were identical with authentic samples prepared following literature methods.

1,6-Dihydropyrazine-2,5-dione (**16**):[23] 95% yield, mp > 320 °C, colourless crystals from ethanol (*Anal*. Calcd for $C_4H_4N_2O_2$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.81; H, 3.62; N, 25.03); ν_{max} (KBr): 3286 br cm^{-1}; δ_H (DMSO-d_6): 8.12 (1H, s, pyrazine H-6), 8.32 (1H, s, pyrazine H-3), 11.34 (2H, br s, hydroxy H); δ_C (DMSO-d_6): 140.98 (pyrazine C-6), 145.77 (pyrazine C-3), 154.42 (pyrazine C-2), 154.67 (pyrazine C-5); MS: m/z 112 (M^+).

3-Phenyl-3a,4,7,7a-tetrahydroisoxazolo[4,5-b]pyrazine-5,6-dione (**20**): 88% yield, mp 171-172 °C, pale yellow crystals from ethyl acetate (*Anal*. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C,

57.21; H, 3.89; N, 17.22); ν_{max} (KBr): 1692, 1674 cm^{-1}; δ_H ($CDCl_3$): 5.42 (1H, dd, J_1 = 7.9 Hz, J_2 = 4.3 Hz, dihydroisoxazole H-4), 5.96 (1H, dd, J_1 = 7.9 Hz, J_2 = 4.0 Hz, dihydroisoxazole H-5), 7.30 (2H, br s amide H), 7.27-7.71 (5H, m, phenyl H), δ_C ($CDCl_3$): 63.78 (dihydroisoxazole C-4), 85.94 (dihydroisoxazole C-5), 127.42, 127.87, 128.34, 130.56 (phenyl C), 155.36 (pyrazindione C-3), 156.12 (pyrazindione C-2) 157.14 (dihydroisoxazole C-3); MS: m/z 231 (M^+).

1,4-Dihydropyrazine-2,3-dione (**23**):[24] 92% yield, mp >330 °C, pale yellow crystals from ethanol (*Anal*. Calcd for $C_4H_4N_2O_2$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.91; H, 3.58; N, 25.03); ν_{max} (KBr): 3420 br cm^{-1}; δ_H (DMSO-d_6): 6.64 (2H, s, pyrazine H-5 and H-6), 11.42 (2H, br s, hydroxy H); δ_C (DMSO-d_6): 119.34 (pyrazine C-4 and C-5), 153.86 (pyrazine C-2 and C-3); MS: m/z 112 (M^+).

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