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REACTIONS OF BENZONITRILE OXIDE WITH METHOXYPYRIMIDINES AND PYRIMIDONES

Antonino Corsaro,*[a] Venerando Pistarà,[a] Antonio Rescifina,[a] Maria A. Chiacchio,[a] Anna Piperno,[b] and Giovanni Romeo[b]

[a]Department of Chemical Science, Catania University, Viale Andrea Doria 6, 95125 Catania, Italy, E-mail: acorsaro@unict.it

[b]Department Pharmaceutical-Chemical, Messina University, Viale SS. Annunziata, 90168 Messina, Italy

Abstract – Methoxypyrimidines preferentially add to benzonitrile oxide to give cycloadducts to their C=N double bonds. These, however, lose benzonitrile affording the corresponding pyrimidones. Cycloadditions to their C=C double bonds take place to a very low extent, and products generally undergo a ring opening process which affords the corresponding oximes. Pyrimidones preferentially give addition products to their nitrogen atoms, and only in the case of 4-pyrimidone, the cycloadduct to its C=C double bond was isolated.

INTRODUCTION

The 5,6-substituted pyrimidine nucleosides, enclosed those with a five- or six-membered heterocycle fused to the pirimidine 5,6-double bond, have drawn the attention of several research groups because of their biological activities, such as antitumor, anti-HIV, anti-HSV and spermicidal activities.[1]

Among the possible strategies for the construction of these unnatural nucleosides, cycloaddition reactions of 1,3-dipoles[2] to the pirimidine C_5=C_6 double bond appear to be the best direct method that involves a small number of synthetic steps.

In connection with one of our research programs on modified nucleosides,[3] we were interested to cover the above synthetic route in order to obtain dihydroisoxazolopyrimidinone or -dione nucleosides by 1,3-dipolar cycloaddition reaction of benzonitrile oxide (**1**) (BNO) with 2-methoxypyrimidine (**2a**) and 4-methoxypyrimidine (**2b**) in the stoichiometric ratio of **1**:**2a**,**b** = 4:1, since it appears from literature, that **1** is inert towards uracil,[4] but **1** reacts with pyrimidine even if it affords products in low yields.[5]

Based on our knowledges acquired within the 1,3-dipolar cycloaddition reactions of nitrile oxides with pyridine[6–8] and diazine systems,[5] our synthetic strategy anticipated the formation of bis- and/or tris-adducts through an initial pseudo-pericyclic process[9] of the nitrile oxide addition to the C=N double bond of pyrimidine derivatives, followed by the 1,3-dipole cycloaddition to their C=C double bond.[5] These bis- and/or tris-adducts undergo, generally, upon exposure to the air and light at room temperature, degradation processes with loss of benzonitrile to give the corresponding pyrimidones and/or -diones.[5,6] Furthermore, these methoxy derivatives can undergo a very ease hydrolysis in acidic or, some times, alkaline medium of the alkoxy group.[10]

However, we have also investigated the route of the reactions of **1** with pyrimid-2(1*H*)-one (**3a**) and -4(3*H* or 1*H*)-one (**3b**) in the stoichiometric ratio of **1**:**3a**,**b** = 6:1, considering that the addition of **1** to pyrazinone[11] as well as pyridone[12] provides *N*- and/or *O*-addition products, of which the last ones are very transient compounds since they spontaneously convert in the corresponding carbamates.[12] Also these can undergo the nitrile oxide cycloaddition to give bis- and/or tris-adducts and then our target molecules after hydrolysis and degradation processes.

Against the availability of starting materials, these processes present the disadvantage of low yields; in our case, however, methoxypyrimidines are expected to be more reactive with respect to the pyrimidine owing to the greater nucleophilicity of their nitrogen atoms directly conjugated with the methoxyl electron-donor group. In order to confirm this latter electronic effect, the work was completed by performing the reaction of **1** with 5-methoxypyrimidine (**2c**), nitrogen atoms of which do not enjoyed the effect of the methoxy group.

Really, the synthesis of this type of ring systems could be accomplished starting from an isoxazoline derivative containing functional groups suitable for the ring closure to the pyrimidine, but this route shows some difficulties and it is considerably longer.[13]

In this paper we report the results of the above investigations which the obtained adducts undergo a further ring opening process of isoxazoline nucleus to give the corresponding oximes such as dichlorobenzonitrile oxide adducts to uracil.[4a]

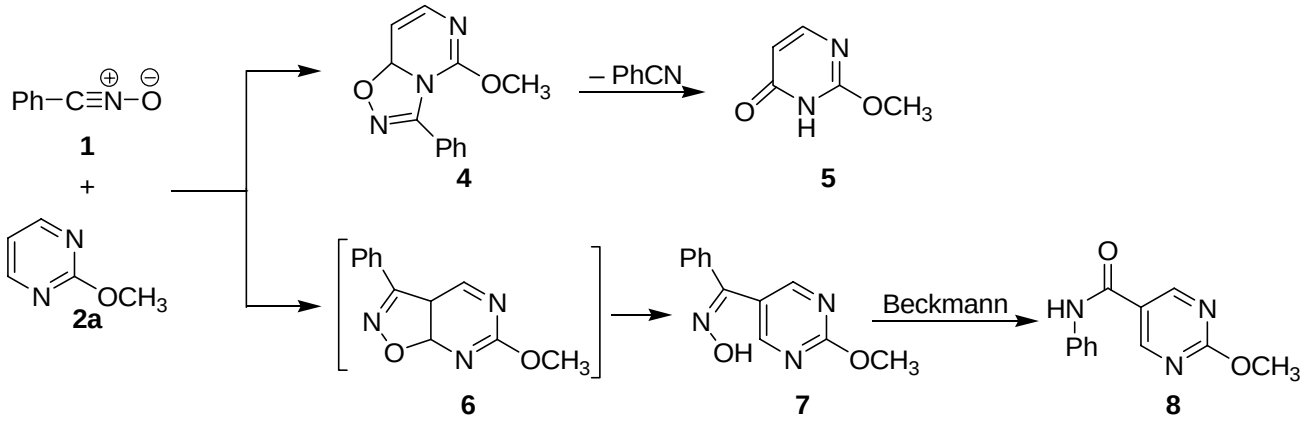
RESULTS AND DISCUSSION

Reactions were conducted by slowly adding triethylamine in anhydrous toluene or methanol to a stirred, ice cooled, solution of pyrimidine derivatives (**2a**–**c**) and benzhydroximic acid chloride in the same solvent over a period of 6 h. After that the room temperature was reached, the reaction mixture was allowed under stirring for one day and then the solvent was removed. The residue was subjected to column or flash chromatography in order to separate unreacted pyrimidine derivatives and nitrile oxide dimers and then a centrifugally enhanced preparative thin layer chromatography (CEPTLC) was used for

the separation of several different products contained in the remaining fractions. Because of their insolubility in toluene, reactions of **1** with **3a**,**b** were conducted only in methanol following the same work-up.

2-Methoxypyrimidine (2a)

The greater nucleophilicity of **2a** with respect to pyrimidine was disclosed by the greater reactivity of its C=N double bond towards **1**. Mainly 5-methoxy-3-phenyl-8a*H*-[1,2,4]oxadiazolo[4,5-*c*]pyrimidine (**4**) (30%) was produced, which spontaneously degrades upon standing in toluene solution to the air and light for two days at room temperature affording quantitatively the already known[14] 2-methoxypyrimidin-4(3*H*)-one (**5**) (Scheme 1). Probably, this latter was also present in the reaction mixture, but in so small amount that it was ignored. The oxadiazolo[4,5-*c*]pyrimidine (**4**) was characterized on the basis of its ^{1}H NMR spectrum which contains three double doublets at 5.59 (J = 1.7 and 3.6 Hz), 5.71 (J = 3.6 and 8.0 Hz) and 6.58 ppm (J = 1.7 and 8.0 Hz) for H-8a, H-8 and H-7 protons, respectively. The ^{13}C NMR spectrum contains signals at 81.29, 114.84, 131.68, 153.85 and 164.70 ppm, which are attributable to C-8a, C-8, C-7, C-3 and C-5 carbons, respectively.



Scheme 1

Minor product was 2-methoxy-5-[(hydroxyimino)phenylmethyl]pyrimidine (**7**) (9%), which was identified on the basis of a singlet at 8.34 ppm characteristic for H-4 and H-6 protons and a broad singlet at 12.26 ppm for the oxime proton in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed signals at 159.47 ppm for H-4 and H-6 carbons and 156.47 ppm for oxime carbon.

The structure of **7** was assigned and its *syn* stereochemistry confirmed by its Beckmann rearrangement,[15] which gave 5-carboxamide derivative (**8**) (65%). Among its ^{1}H NMR signals**,** that of the amide proton at 8.75 ppm was apparent, while that of the oxime proton at 12.26 ppm was disappeared. Its ^{13}C NMR spectrum was also diagnostic since this contained a new signal at 165.37 ppm for the amide carbon. Its IR spectrum contained the absorption band of the amide carbonyl group at 1664 cm^{-1}.

In the light of Ryu's work,[4a] the oxime (**7**) could be generated from the initially formed 1,3-cycloadduct (**6**), which spontaneously undergoes a ring opening process into **7**. We tried to isolate or trap **6** by the

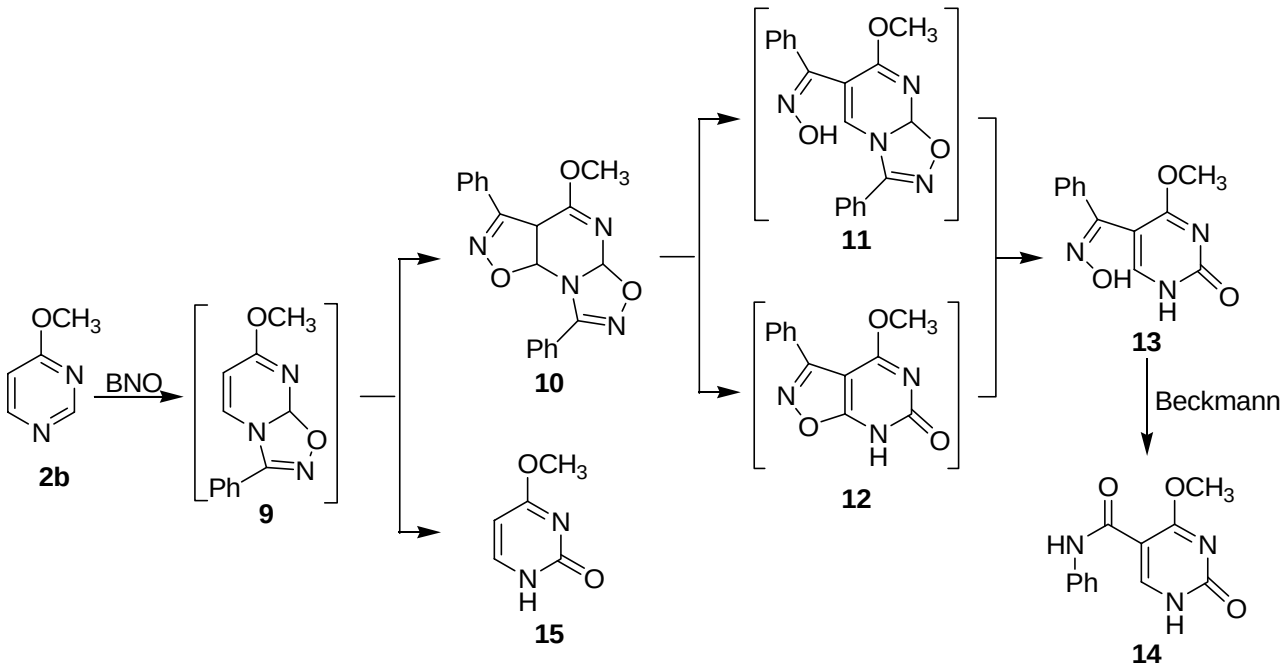
same benzonitrile oxide or other 1,3-dipoles or dienes, but without success. The sole evidence for the initial formation of **6** was that deriving from ^{1}H NMR spectral experiments conducted after 5 h on the initial reaction mixture. These showed a very weak apparition of a double doublet at 4.45 ppm and a doublet at 6.42 ppm for H-5 and H-4 protons, respetively.

When the reaction was conducted in methanol as solvent, somewhat lower yields of **4** (12%) and **7** (5%) were obtained, together with a small amount of **5** (2%).

4-Methoxypyrimidine (2b)

The main product of the reaction between **1** and **2b** was isoxazolo[4,5-*e*][1,2,4]oxadiazolo[4,5-*a*]-pyrimidine (**10**, 26%), the structure of which was inferred by its ^{1}H and ^{13}C NMR spectra (Scheme 2). ^{1}H NMR signals were two doublets at 4.42 and 6.15 ppm with the characterictic coupling constant (J = 8.9 Hz) of *cis* isoxazolines[16] and a singlet at 6.69 ppm for the H-5 oxadiazole proton. Three ^{13}C NMR signals at 45.62, 83.84, and 97.15 ppm were diagnostic of C-3a, C-9a, and C-5a carbons, respectively.

Minor products were the already known[17] 4-methoxypyrimidin-2(1*H*)-one (**15**, 8%) and 5-[(hydroxyimino)(phenyl)methyl]-4-methoxypyrimidin-2(1*H*)-one (**13**, 7%), the IR spectrum of which shows the peculiar bands at 3478 (br) and 1672 cm^{-1}. Its ^{1}H NMR spectrum shows the H-6 proton as singlet at 8.47 ppm together with the amide and oxime protons at 9.23 and 12.30 ppm as broad singlets, respectively. Its ^{13}C NMR spectrum showed signals at 153.93 and 160.02 ppm attributable to the oxime and carbonyl carbons, respectively.



Scheme 2

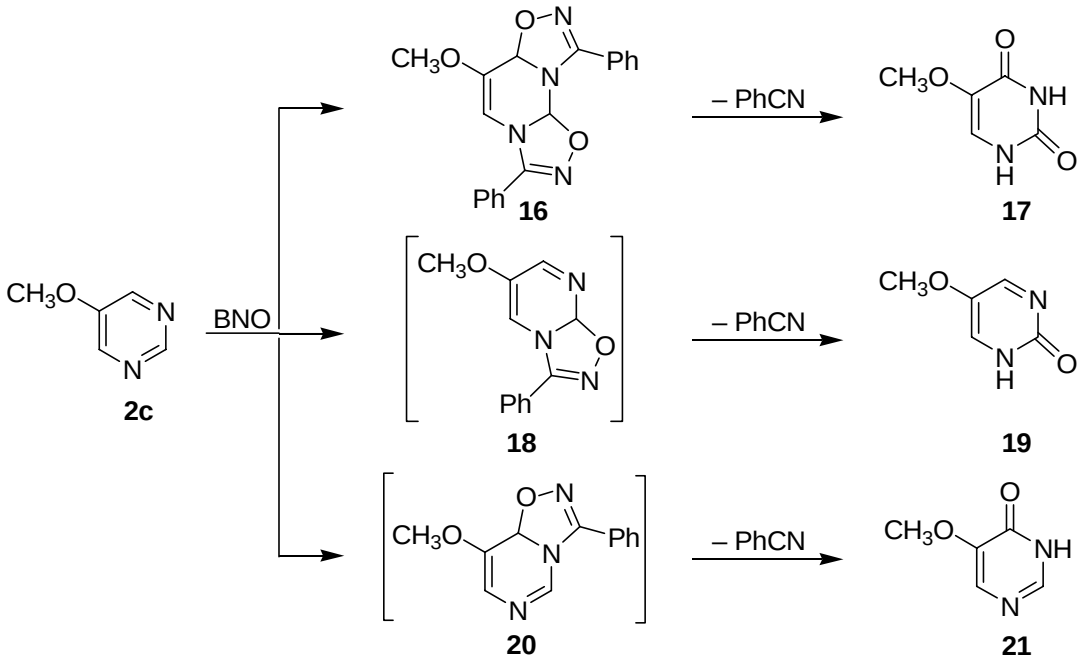
The production of **10** was indicative of the initial formation of the non isolable cycloadduct (**9**), which partly degrades into **15** by losing benzonitrile and partly undergoes a second cycloaddition of **1** to its C=C

double bond affording **10**. Also **10** undergoes the two degradation and ring opening of isoxazoline nucleus processes to give **13**, so as it was verified by means of the conversion of **10** into **13** keeping a toluene solution of **10** at room temperature to the air and light for two days. Intermediates of these two processes can be both **11** and **12**. The structure and stereochemistry of **13** was assigned also by its conversion into **14** (63%) by means of the Beckmann rearrangement[15] (Scheme 2).

The distribution of reaction products in methanol was different, since only the oxime (**13**, 4%) and pyrimidone (**15**, 12%) were isolated.

5-Methoxypyrimidine (2c)

Reaction mixture TLCs of **2c** with **1** in the two used solvents presented, after *ca*. 7 h, two spots with R_f lower than that of dimers. These, successively, turned yellow and then, after a day, disappeared. Our attempts to isolate or trap, with different cycloaddition reactions, the compounds corresponding to these two spots failed. From CEPTLC of the work-up reaction mixtures, oxadiazolo[4,5-*a*:4',5'-*c*]pyrimidine (**16**) and a mixture consisting of the two known isomer 5-methoxypyrimidin-2- (**19**)[18] and -4-one (**21**)[19] in very low yields (**16**, 10%; **19**, 8%; **21**, 5%) was isolated. The structure of **16** was arisen from its ^{1}H and ^{13}C NMR spectral data and from its conversion into 5-methoxyuracil (**17**) by keeping **16** for two days to the air and light in methanol solution at room temperature. The ^{1}H NMR spectrum of **16** was characterized by a singlet at 5.89 ppm for the H-5 proton, H-10a and H-6a protons being covered by phenyl proton signals. ^{13}C NMR signals were found at 79.86 and 94.36 ppm for C-6a and C-10a carbons, at 110.22 ppm for the olefinic C-5 carbon and at 155.24 and 159.29 ppm for C-9 and C-3 carbons, respectively.



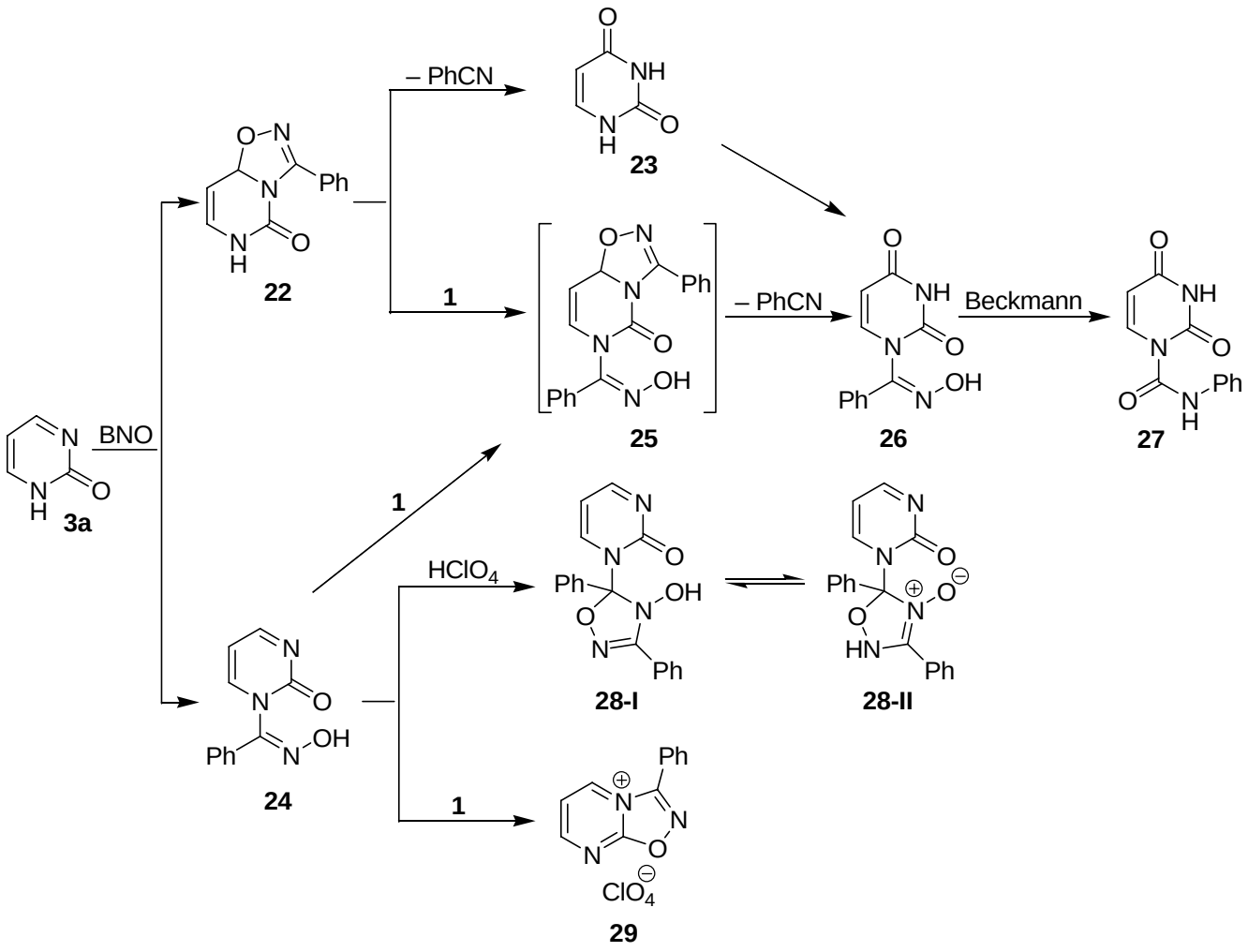
Scheme 3

The two methoxypyrimidones (**19**) and (**21**) were easily identified thorugh their ^{1}H and ^{13}C NMR spectral data compared with those of authentical samples. They were generated from the two initially formed cycloadducts (**18**) and (**20**), which successively fragment losing benzonitrile to give **19** and **21**, respectively, or add a second molecule of **1** to give the bisadduct (**16**) (Scheme 3).

Pyrimid-2(1*H*)-one (3a)

The exposure of **3a** to **1** in methanol solution afforded the already known cycloadduct (**22**, 60%)[5] which was separated by flash chromatography, identified by comparison of its spectral data with those of an authentical sample, and further confirmed by its spontaneous quantitative conversion into uracil (**23**) on standing in the same solution at room temperature to the air and light for two days.

The CEPTLC of residual fractions allowed the separation of addition products (**24**, 9%) and (**26**, 4%) to the N-1 nitrogen atom of **3a** and uracil, respectively, and bicyclic product (**28**, 3%) (Scheme 4).



Scheme 4

The structure of **24** was identified on the basis of its IR, ^{1}H and ^{13}C NMR spectra. Its IR spectrum is characterized by absorptions bands at 3448 br and 1674 cm^{-1} which are attributable to the oxime hydroxy and carbonyl groups, respectively. Its ^{1}H NMR spectrum contains a triplet at 5.93 ppm (J = 8.3 Hz) for

the H-5 proton, two double doublets at 8.02 and 9.48 ppm (J = 8.3 and 1.7 Hz) for H-6 and H-4 protons, respectively, and a broad singlet at 12.07 ppm for the oxime proton. In its ^{13}C NMR spectrum, the signal of an oxime carbon at 154.20 ppm in addition to that of carbonyl group at 169.16 ppm are evident.

Furthermore, its structure was assigned based on its easy conversion into the corresponding isoxazolopyrimidinium salt (**29**) by treatment with perchloric acid. The salt was identified through the disappearance of the signal of carbonyl carbon in the ^{13}C NMR spectrum and that of the oxime proton in the ^{1}H NMR spectrum. The shift to lower fields of the three pyrimidine protons were also apparent.

The bicyclic compound (**28**) derives from the cycloaddition of a second molecule of **1** to the C=N double bond of **24**, and it exists as mixture of two isomers (**28-I**) and (**28-II**) in the ratio of **28-I**:**28-II** = 65:35, so as it appears from its ^{1}H and ^{13}C NMR spectra. Indeed, the first shows two broad singlets at 10.22 and 10.69 ppm for the hydroxy and oxadiazole protons and the second shows two signals for the oxadiazole C-5 carbons at 93.83 and 99.79 ppm and C-3 carbons at 144.88 and 156.63 ppm.

The pyrimidin-2,4(1*H*,3*H*)-dione oxime (**26**) was identified through its ^{1}H NMR spectrum where a broad signal at 11.14 for the N-H proton was evident; the appearance of two signals at 166.20 and 168.24 ppm for C-4 and C-2 carbonyl carbons, respectively, was in the ^{13}C NMR spectrum, and the IR spectrum contains two absorption bands attributable to carbonyl groups at 1676 and 1680 cm^{-1}. Furthermore, its structure and stereochemistry was realized by means of its conversion into the amide **27** by the Beckmann rearrangement.[15]

The oxime (**26**) originated, as it was verified, by addition of a second molecule of **1** to the N-1 nitrogen atom of **23** or by loss of benzonitrile from the non isolable **25**. The oxime (**25**) in its turn can be originated by addition of a second molecule of **1** to the N-1 nitrogen atom of **22** or to the C=N double bond of **24**.

Pyrimid-4(3*H*)- or pyrimid-4(1*H*)-one (3b)

The two lactam forms, pyrimidin-4(1*H*)-one (**3b-I**) and pyrimidin-4(3*H*)-one (**3b-II**) exist in equilibrium with 4-hydroxypyrimidine (**3b-III**). The first two compounds are known to be favored in the crystalline state and solutions,[20] whereas the contribution of **3b-III** to the equilibrium should become comparable to that of the keto forms in the gaseous phase.[20a] From previous estimations based on ultraviolet,[21] IR and Raman[22] and ^{1}H and ^{13}C NMR[23] spectroscopy it is concluded that the main species (more than 80%) present in aqueous solutions is **3b-II** and, furthermore, because this percentage is naturally dependent on the dielectric constant of solvent, it is expected that it is progressively shifted toward the isomer (**3b-II**) in water-ethanol solutions as the ethanol content is increased[23a] (Scheme 5).

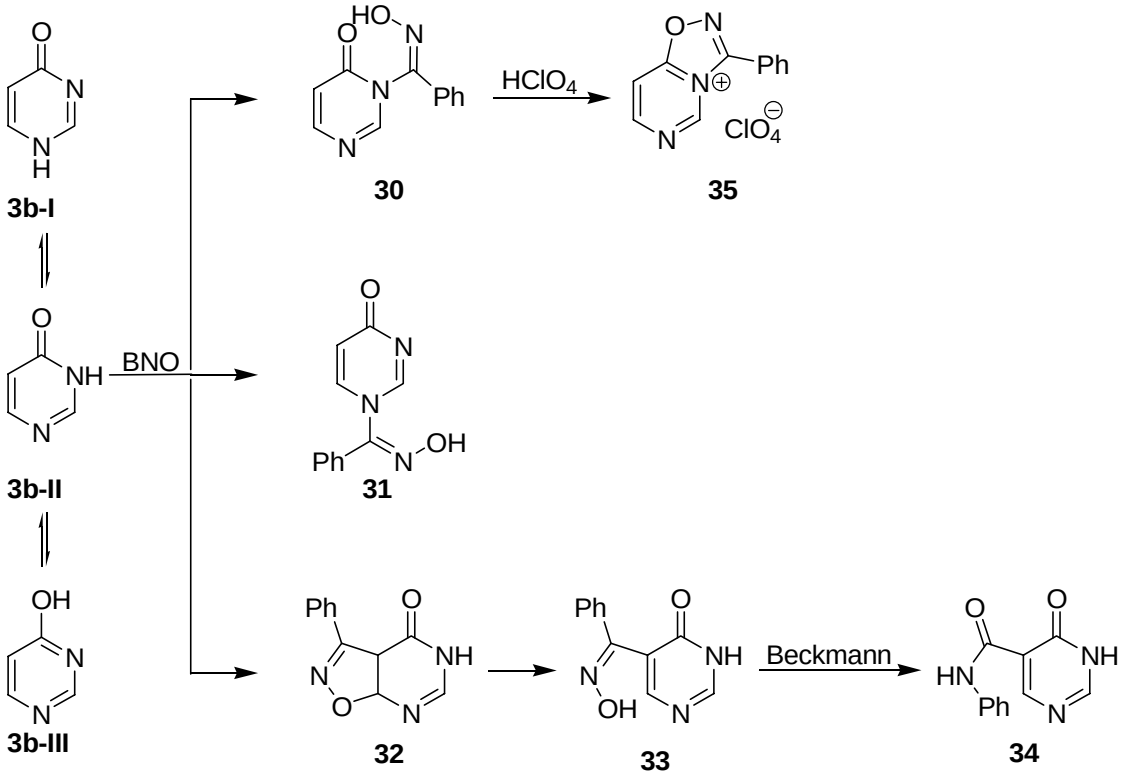
These observations were confirmed by our results based on its chemical reactivity.

Upon reaction of **3b** with **1** the initial flash chromatography afforded adduct (**30**, 40%) to the N-3 nitrogen atom along with small amounts of adduct (**31**, 6%) to the N-1 nitrogen atom. Successively,

CEPTLC has allowed to isolate isoxazolo[5,4-*d*]pyrimid-4-one (**32**) in very low yield (5%) together with other amounts of adducts (**30**, 5%) and (**31**, 2%) (Scheme 5).

Oximes (**30**) and (**31**) were characterized by the oxime proton in the range 12.36–12.40 ppm in the ^{1}H NMR spectra and by oxime and carbonyl carbon atoms in the range 154.20–155.71 ppm and 164.46–164.85 ppm, respectively, in the ^{13}C NMR spectra. The oxime (**30**) was differentiated starting from **31** by the obtainment of **35** upon treatment of **30** with perchloric acid. The obtained salt (**35**) was identified by two doublets at 7.71 (J = 7.6 Hz) and 9.54 ppm (J = 0.9 Hz) for H-8 and H-5 protons, respectively, and a double doublet at 9.01 (J = 0.9 and 7.6 Hz) for the H-7 proton in the ^{1}H NMR spectrum.

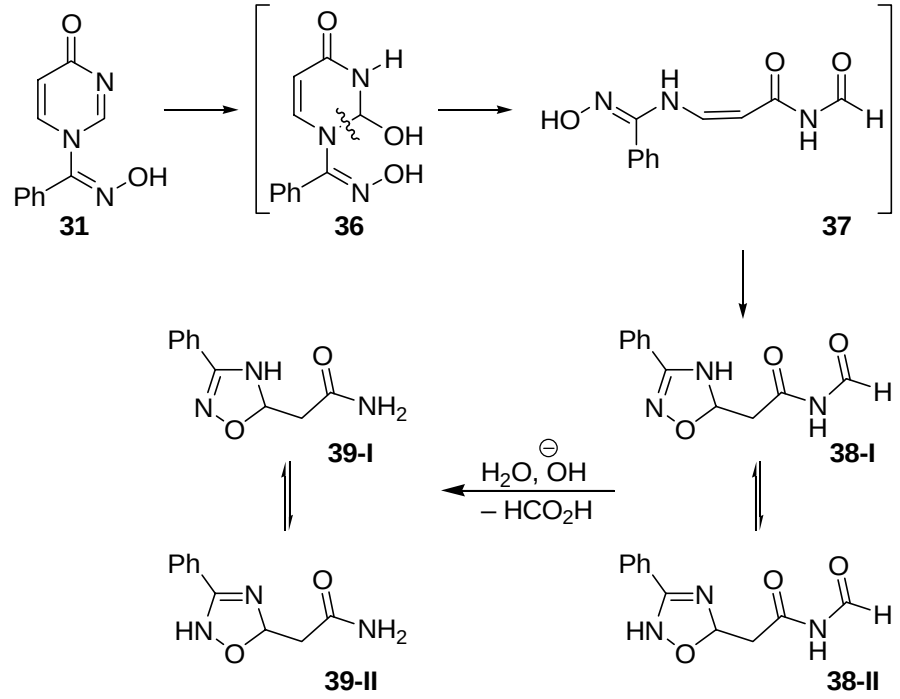
The dihydroisoxazole[5,4-*d*]pyrimid-4-one (**32**) was identified on the basis of its ^{1}H and ^{13}C NMR spectra. The first contains three doublets at 5.00, 6.96, and 9.06 ppm (J = 8.2 Hz) for H-3a, H-7a, and H-6 protons, respectively, and a broad doublet at 11.05 ppm for the N-H proton. The second confirms the assigned structure containing signals at 59.84 and 91.41 ppm for C-3a and C-7a carbons, 153.73 and 166.84 ppm for the oxime C-3 and carbonyl C-9 carbons, respectively.



Scheme 5

On standing in methanol solution **32** undergoes the ring opening process of isoxazoline nucleus to give the oxime (**33**) easily identifiable by ^{1}H NMR signals at 8.43 and 12.18 ppm for H-6 and oxime protons and the ^{13}C NMR signal at 154.76 ppm for the C-6 carbon. Its structure and stereochemistry was further realized by means of its conversion by the Beckmann reaction[15] into the amide (**34**) identified through its

^{13}C NMR signal at 164.11 ppm of the new amide carbon atom and its IR absorption bands at 3346, 1680, 1636 cm^{-1}.



Scheme 6

Probably, owing to the use of not dried solvents and/or silica gels, the first attempt of CEPTLC afforded 8% of the oxime (**30**) and 9% (global yield) of *N*-formyl-2-(3-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)-acetamide (**38-I**) in equilibrium with its 2,5-dihydro isomer (**38-II**), which are originated from the hydration[24] of **31** into **36**. This latter undergoes an opening ring process to give **37**, which, finally, recloses into the oxadiazoline nucleus (Scheme 6).

There were NMR spectral evidences for the mixture of two inseparable forms (**38-I**) and (**38-II**) in the equilibrium ratio of 89:11. Besides the two doublets at 9.08 and 10.17 ppm of formyl and imidic proton, respectively, ^{1}H NMR signals in deuterated acetone were at 2.60 (dd, methylene Ha), 2.69 (dd, methylene Hb), 5.97 (m, oxadiazole H-5) and 6.62 (br s, N-H) ppm for **38-I**, while those of **38-II** were at 2.92 (dd, methylene Ha), 2.98 (dd, methylene Hb), 6.12 (m, oxadiazole H-5) and 6.74 (br s, N-H) ppm. ^{13}C NMR signals at 42.64 and 43.94 ppm were attributable to the two methylenic carbons, those at 90.27 and 91.30 ppm to the two C-5 oxadiazole carbons. The IR spectrum shows one broad intense bands at 3440 cm^{-1}, and two bands at 1640 and 1628 cm^{-1}. This amide was furthermore characterized by selective hydrolysis of the *N*-formyl group to afford the primary amide (**39**, 92%) as shown by the disappearance of the formyl proton and carbonyl carbon atom in ^{1}H NMR and ^{13}C NMR spectra, respectively.

Probably, in spite of what happens in the reaction of pyrimidine with **1**, the steric congestion of the transition state owing to the 2-methoxy group, prevents the formation of bis-adducts in the reaction of **2a** with **1** and therefore the sole reaction products are **4** and **7**, which derives from the non isolable **6**. The

monocycloadduct (**4**), too, is converted into **5**, but this process is slower than the ring-opening process of **6**. All our attempts made in order to isolate or trap **6** failed.

Besides a low yield (8%) of **15**, 4-methoxypyrimidine (**2b**) affords a modest yield (26%) of bis-adduct (**10**), which spontaneously undergoes the two process of isoxazole ring-opening and loss of benzonitrile to give **13** without allowing the isolation of dihydroisoxazolopyrimidindione (**12**), which was another molecular target.

For these reasons, dihydroisoxazolopyrimidines can not be obtained by cycloadditions of **2a**,**b** with **1**, but only the oximes, which can be useful intermediates for the synthesis of a variety of other compounds such as for example isoxazolopyrimidinium salts.[25] As it was expected, 5-methoxypyrimidine (**2c**) affords monoadducts (**18**) and (**20**) and the bis-adduct (**16**) in very low yield. These, however, lose benzonitrile to give the corresponding pyrimidones (**19**) and (**21**) and pyrimidindione (**17**).

In addition to the already known **22** obtained with a satisfactory yield, the reaction of **3a** with **1** has not permitted the obtainment of addition products to the C_5=C_6 double bond of pyrimid-2-one.

On the contrary, the reaction of **3b** with **1** was the unique one that has led to an isolated dihydroisoxazolopyrimidone, even if in very low yield, together with the expected *N*-adducts (**30**) and (**31**). The bicyclic compound (**32**) presents a greater stability with respect to **6**, but, however, it is easily susceptible of opening its isoxazole ring.

CONCLUSION

In conclusion, pyrimidine derivatives under investigation preferentially add benzonitrile oxide to give cycloadducts to their C=N double bonds with exception of **3b** which affords only addition products to its nitrogen atoms. Cycloadducts to their C=C double bonds are very weak compounds, and therefore, the synthetic route followed by us for dihydro- and isoxazolopyrimidinones or diones discloses its limitations.

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 and ^{13}C NMR spectra were recorded on a Varian Unity Inova (500 MHz for the proton and 125 MHz for the carbon spectra) spectrometers using tetramethylsilane as internal standard and $CDCl_3$ or DMSO-d_6 as solvents. All proton and carbon signals were full assigned by 2D homo- and heteronuclear correlation spectroscopy (gCOSY and gHSQC). IR spectra were obtained on a Perkin Elmer Paragon 500 FT IR spectrophotometer by using potassium bromide discs or nujol mulls and mass spectra were registered 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[26] using Merck silica gel 60 and centrifugally enhanced preparative thin layer chromatography (CEPTLC) using Merck silica gel 60 PF_{254}. Mixtures of cyclohexane-toluene, toluene-ethyl acetate and ethyl acetate-methanol were used as eluents with a rising gradient towards the most polar eluent.

Starting materials

Benzhydroximic acid chloride[27] (**2a**,[28] **2b**,[29] and **2c**[30]) were prepared following established literature procedures. Pyrimidone (**3a**) as its hydrochloride and **3b** are commercial compounds and have been purchased from the Aldrich Co. Solvents and eluents for the chromatography were dried following literature procedures.[31] The identification of samples deriving from different experiments was secured by mixed melting points and IR and ^{1}H NMR spectra.

General procedure for reactions of 1 with pyrimidine derivatives (2a–c) and (3a,b)

To a stirred, ice cooled, solution of benzhydroximic acid chloride (5 g, 32 mmol) and methoxypyrimidines (**2a**–**c**) (0.9 g, 8 mmol) in anhydrous toluene (100 mL), triethylamine (4.5 mL, 32 mmol) in the same solvent (20 mL) was added over a period of 1 h and then the reaction mixture was allowed to reach rt. After one day of stirring, the solvent was removed and the residue was subjected to gravity or flash chromatography with which unreacted **2a**–**c** and dimers of **1** were generally separated as predominant compounds. Residues of remaining fractions were then cromatograpfed by CEPTLC.

These reactions were then repeated in anhydrous CH_3OH solution under the same conditions. Because of their insolubility in toluene, reactions of **3a**,**b** with **1** under the stoichiometric ratio of **1**:**3a**,**b** = 6:1 were conducted only in anhydrous CH_3OH under the same conditions.

Reactions of 1 with 2a

By CEPTLC of the residue of fractions not containing unreacted **2a** and dimers of **1**, oxadiazolo[4,5-c]pyrimidine (**4**), and pyrimid-2-one oxime (**7**) were isolated together with other products in so small amounts that they were ignored.

5-Methoxy-3-phenyl-8a*H*-[1,2,4]oxadiazolo[4,5-*c*]pyrimidine (4). 30% yield, mp 142–143 °C, from ethyl acetate. Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.71; H, 4.82; N, 18.40. ^{1}H NMR (DMSO-d_6): δ 3.86 (3H, s, methoxyl H), 5.59 (1H, dd, J = 1.7, 3.6 Hz, H-8a), 5.71 (1H, dd, J = 3.6, 8.0 Hz, H-8), 6.58 (1H, dd, J = 1.7, 8.0 Hz, H-7), 7.32–7.58 (3 H, m, phenyl H), 7.66–8.04 (2H, m, phenyl H). ^{13}C NMR (DMSO-d_6): δ 54.76 (methoxyl C), 81.29 (C-8a), 114.84 (C-8), 128.87, 130.45, 131.36, 131.68, 133.53 (C-7 and phenyl C), 153.85 (C-3), 164.70 (C-5). MS (EI): *m/z* 229, (M^+).

2-Methoxy-5-[(*Z*)-(hydroxyimino)(phenyl)methyl]pyrimidine (7). 9% yield, mp 129–130 °C, from ethyl acetate. Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.69; H, 4.83; N, 18.37. IR (KBr): ν_{max} 3444 br cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.92 (3H, s, methoxyl H), 7.38–7.58 (3H, m,

phenyl H), 7.62–7.75 (2H, m, phenyl H), 8.34 (2H, s, H-4 and H-6), 12.26 (1H, br s, oxime H, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 54.48 (methoxyl C), 129.92, 131.38, 132.14, 149.65 (phenyl C), 156.47 (oxime C), 159.47 (C-4 and C-6), 163.96 (C-2). MS (EI): *m/z* 229, (M^+).

The same product distribution was observed in CH_3OH, but with somewhat lower little yields for **4** (12%) and **7** (5%). Also **5** was isolated in trace amounts.

Reactions of 1 with 2b

The CEPTLC has allowed to isolate the following products in the stated yields in this order:

4-Methoxypyrimidin-2(1*H*)-one (15). 26% yield, identical in mp, IR and ^{1}H NMR spectra with those of a sample prepared according to the literature.[17]

3,8-Diphenyl-4-methoxy-3a,9a-dihydro-5a*H*-isozazolo[4,5-*e*][1,2,4]oxadiazolo[4,5-*a*]pyrimidine (10). 8% yield, mp 176–178 °C, from ethyl acetate. Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 62.29; H, 4.62; N, 16.12. ^{1}H NMR ($CDCl_3$): δ 3.78 (3H, s, methoxy H), 4.42 (1H, d, J = 8.9 Hz, H-7a), 6.15 (1H, s, H-4a), 6.69 (1H, d, J = 8.9 Hz, H-9a), 7.42–7.78 (10H, m, phenyl H). ^{13}C NMR ($CDCl_3$): δ 45.62 (C-3a), 54.26 (methoxy C), 83.84 (C-7a), 97.15 (C-9a), 127.48, 128.48, 128.76, 129.12, 131.04, 131.32, 132.01, 134.86 (phenyl C), 153.39 (C-7), 155.78 (C-3), 164.90 (C-8). MS (EI): *m/z* 348, (M^+).

5-[(Hydroxyimino)(phenyl)methyl]-4-methoxypyrimidin-2(1*H*)-one (13). 7% yield, mp 135–137 °C, from ethyl acetate. Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.96; H, 4.53; N, 17.11. IR (KBr): ν_{max} 3478 br, 1672 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.04 (3H, s, methoxyl H), 7.44–7.49 (2H, m, phenyl H), 7.66–7.88 (3H, m, phenyl H), 8.47 (1H, d, J = 6.0 Hz, H-6), 9.23 (1H, d, J = 6.0 Hz, N_1-H, D_2O-exchangeable), 12.30 (1H, br s, oxime H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 54.98 (methoxyl C), 116.64 (C-5), 127.45, 128.82, 130.69, 134.90 (phenyl C), 149.82 (C-6), 153.93 (oxime C), 158.02 (C-4), 160.02 (C-2). MS (EI): *m/z* 245, (M^+).

From the reaction mixture conducted in CH_3OH only **13** (4%) and **15** (12%) were isolated.

Reaction of 1 with 2c

The flash chromatography has allowed to isolate bisadduct (**16**) and a mixture consisting of 5-methoxypyrimidin-4(3*H*)-one (**19**)[19,] (5% yield) and 5-methoxypyrimidin-2(1*H*)-one (**21**)[18] (8% yield), which were separated by CEPTLC and then easily identified by comparison of their mps, IR, ^{1}H NMR spectrum with those of samples prepared according to the literature.

6-Methoxy-3,9-diphenyl-6a*H*-bis[1,2,4]oxadiazolo[4,5-*a*:4',5'-*c*]pyrimidine (16). 10% yield, mp 170–172 °C, from ethyl acetate. Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.41; H, 4.62; N, 16.11. ^{1}H NMR ($CDCl_3$): δ 3.96 (3H, s, methoxyl H), 5.89 (1H, s, H-6a), 7.04–7.58 (8H, m, H-5, H-10a, and phenyl H), 7.64–7.82 (4H, m, phenyl H). ^{13}C NMR ($CDCl_3$): δ 54.65 (methoxyl C), 79.86 (C-6a), 94.36 (C-10a), 112.22 (C-5), 124.43, 126.34, 129.74, 129.92, 130.35, 130.79, 132.25,

134.48, 136.58 (phenyl C), 155.24 (C-9), 159.29 (C-3), 164.28 (C-6). MS (EI): *m/z* 348, (M^+).

Reaction of 1 with 3a

The flash chromatography of the reaction mixture conducted in CH_3OH afforded the cycloadduct (**22**, 60%) identical to that previously obtained by the same reaction conducted in CH_2Cl_2.[5] This, on standing one day in CH_3OH solution in the presence of air and light at rt, quantitatively degrades into benzonitrile and uracil, identical with authentical samples.

The residual mixture of products was furthermore separated by means of CEPTLC to give mainly oximes (**24**) and **(26**), and bisadduct (**28**).

1-[(*Z*)-(Hydroxyimino)(phenyl)methyl)]pyrimidin-2(1*H*)-one, (24). 9% yield, mp 128–130 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.30; H, 4.22; N, 19.57). IR (KBr): ν_{max} 3448 br, 1674 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.93 (1H, t, J = 8.3 Hz, H-5), 7.47–7.52 (3H, m, phenyl H), 7.85–7.98 (2H, m, phenyl H), 8.02 (1H, dd, J = 1.7, 8.3 Hz, H-6), 9.48 (1H, dd, J = 1.7, 8.3 Hz, H-4), 12.07 (1H, br s, oxime H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 106.21 (C-5), 128.86, 129.15, 131.57, 134.90 (phenyl C), 154.20 (oxime C), 156.93 (C-4), 166.24 (C-6), 169.16 (C-2). MS (EI): *m/z* 215, (M^+).

1-(4-Hydroxy-3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)pyrimidin-2(1*H*)-one (28-I) in mixture with 1-(4-oxido-3,5-diphenyl-2,5-dihydro-1,2,4-oxadiazol-5-yl)pyrimidin-2(1*H*)-one (28-II). (**28-I**:**28-II** = 65:35): 3% global yield, mp 144–148 °C, from ethyl acetate. Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 61.89; H, 4.23; N, 16.74. IR (KBr): ν_{max} 3260 br, 1668 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.94 (1H, t, J = 5.5 Hz, pyrimidone H-5), 7.10 (1H, d, J = 5.5 Hz, pyrimidone H-4), 7.36–7.48 (6H, m, phenyl H), 7.89–8.14 (5H, m, phenyl H, pyrimidone H-6), 10.22 (1H, br s, hydroxyl H, D_2O-exchangeable) 10.69 (1H, br s, N-H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 93.83 (**28-I** oxad. C-5), 99.72 (**28-II** oxad. C-5), 102.42 (pyrimidone C-5), 124.73, 126.36, 128.66, 129.45, 130.31, (phenyl C), 133.77 (pyrimidone C-4), 148.88 (**28-I** oxad. C-3), 156.62 (**28-II** oxad. C-3), 162.80 (pyrimidone C-6), 164.34 (pyrimidone C-2). MS (EI): *m/z* 334, (M^+).

1-[(*Z*)-(Hydroxyimino)(phenyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (26). 4% yield, mp 134–136 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.32; H, 3.93; N, 18.12). IR (KBr): ν_{max} 3478 br, 1676, 1680 cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.26 (1H, d, J = 7.8 Hz, H-5), 7.33–7.50 (3H, m, phenyl H), 7.55–8.02 (2H, m, phenyl H), 7.86 (1H,d, J = 7.8 Hz, H-6), 11.14 (1H, br s, amide N-H, D_2O-exchangeable), 12.46 (1H, br s, oxime H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 102.28 (C-5), 127.76, 128.74, 130.40, 133.89 (phenyl C), 155.18 (oxime C), 158.29 (C-6), 166.20 (C-4), 168.24 (C-2). MS (EI): *m/z* 231, (M^+).

Reaction of 1 with 3b

The flash chromatography of the reaction mixture afforded amidoxime (**30**) together with minor amount

of its isomer (**31**) and a mixture of isoxazolo[5,4-*d*]pyrimidone (**32**) and the corresponding oxime (**34**), which were separated by CEPTLC.

3-[(*Z*)-(Hydroxyimino)(phenyl)methyl]pyrimidin-4(3*H*)-one (30). 45% yield, mp 169–171 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.31; H, 4.20; N, 19.57. IR (KBr): ν_{max} 3446 br, 1670 cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.58 (1H, d, J = 6.7 Hz, H-5), 7.44–7.50 (3H, m, phenyl H), 7.58–7.63 (2H, m, phenyl H), 8.05 (1H, d, J = 6.7 Hz, H-6), 8.36 (1H, s, H-2), 12.40 (1H, br s, oxime H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 102.28 (C-5), 127.76, 128.74, 130.40, 133.89 (phenyl C), 152.18 (C-2), 155.71 (oxime C), 158.96 (C-6), 164.85 (C-4). MS (EI): *m/z* 215, (M^+).

1-[(*Z*)-(Hydroxyimino)(phenyl)methyl]pyrimidin-4(1*H*)-one (31). 6% yield, mp 142–144 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.50; H, 4.20; N, 19.45. IR (KBr): ν_{max} 3432 br, 1664 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.87 (d, 1H, J = 7.4 Hz, H-5), 7.73 (1H, d, J = 7.4 Hz, H-6), 7.45–7.58 (3H, m, phenyl H), 7.84–8.02 (2H, m, phenyl H), 8.12 (1H, s, H-2), 12.36 (1H, br s, oxime H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 105.41 (C-5), 130.09, 130.41, 132.21, 139.34 (phenyl C), 154.20 (oxime C), 154.66 (C-6), 158.89 (C-2), 164.46 (C-4). MS (EI): *m/z* 215, (M^+).

3-Phenyl-5,7a-dihydroisoxazolo[5,4-*d*]pyrimidin-4(3a*H*)-one (32). 5% yield, mp 137–139 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.29; H, 4.22; N, 19.47. IR (KBr): ν_{max} 3438 br, 1674 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.00 (1H, d, J = 8.2 Hz, H-3a), 6.96 (1H, d, J = 8.2 Hz, H-7a), 7.12–7.29 (m, 2H, phenyl H), 7.46–7.50 (m, 3H, phenyl H), 9.06 (1H, s, H-6), 11.05 (br d, 1H, N5-H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 59.84 (C-3a), 91.41 (C-7a), 127.32, 128.36, 130.26, 131.30, 153.96 (C-3), 157.68 (C-6), 166.34 (C-4). MS (EI): *m/z* 215, (M^+).

5[(*Z*)-(Hydroximimo)(phenyl)methyl]pyrimidin-4(3*H*)-one (33). 3% yield, mp 163–165 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.62; H, 4.23; N, 19.50. IR (KBr): ν_{max} 3412 br, 1668 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.17–7.58 (3H, m, phenyl H) 7.86–8.09 (2H, m, phenyl H), 8.43 (1H, s, H-6), 8.85 (1H, H-2), 10.19 (1H, br s, N-H, D_2O-exchangeable), 12.18 (1H, br s, oxime H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 101.98 (C-5), 128.72, 130.81, 131.37, 136.09 (phenyl C), 150.64 (C-6), 152.54 (C-2), 154.76 (oxime C), 162.84 (C-4); MS (EI): *m/z* 215, (M^+).

Owing to the use of not dried eluents and/or silica, the first tentative of CEPTLC of the residue of fractions not containing unreacted **3b** and dimers of **1** afforded, in addition to the two oximes (**30**, 38%) and (**33**, 4%), *N*-formyl acetamide (**38**) consisting of inseparable two isomers (**38-I**) and (**38-II**) as shown by its ^1H and ^{13}C NMR spectra.

***N*-Formyl-2-(3-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)acetamide (38-I) in mixture with *N*-Formyl-2-(3-phenyl-2,5-dihydro-1,2,4-oxadiazol-5-yl)acetamide (38-II).** (**38-I**:**38-II** = 7:13): 9% global yield, mp 137–141 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N,

18.02. Found: C, 56.85; H, 4.79; N, 17.95). IR (KBr): ν_{max} 3440 br, 1640, 1628 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.60 (dd, 1H, J = 6.5, 14.5 Hz, 2H-oxad. H-a), 2.92 (1H, dd, J = 5.5, 15.5 Hz, 4H-oxad. H-a), 2.69 (1H, dd, J = 4.5, 14.5 Hz, 2H-oxad. H-b), 2.98 (1H, dd, J = 5.0, 15.5 Hz, 4H-oxad. H-b), 5.97 (1H, m, 2H-oxad. H-5), 6.12 (1H, m, 4H-oxad. H-5), 6.62 (1H, br s, 2H-oxad. N-H, D_2O-exchangeable), 6.74 (1H, br s, 4H-oxad. N-H, D_2O-exchangeable), 7.43–7.73 (3H, m, phenyl H), 7.74–7.76 (2H, m, phenyl H), 10.17 (1H, br s, N-H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 42.64 (2H-oxad. methylene C), 43.94 (4H-oxad. methylene C), 90.26 (2H-oxad. C-5), 101.29 (4H-oxad. C-5), 126.92, 127.34, 129.56, 131.38, 131.53 (phenyl C), 160.52 (2H-oxad. C-3), 162.76 (4H-oxad. C-3), 167.47 (formyl C), 171.43 (amide C). MS (EI): *m/z* 233, (M^+).

Alkaline hydrolysis of *N*-formyl acetamide (38)

N-Formyl amide (**38)** (100 mg, 1 mmol) was dissolved in 1M NaOH/dioxane (1:1 mixture, 5 mL) and stirred for 2 h at 60 °C. After cooling the reaction mixture was neutralized with 1M HCl (5 mL) and extracted with chloroform (2 × 5 mL). The combined organic extracts, dried on anhydrous Na_2SO_4, were concentrated in vacuum to give the crude amide (**39**), which was then recrystallized.

2-(3-Phenyl-4,5-dihydro-1,2,4-oxadiazolol-5-yl)acetamide (39-I) in mixture with 2-(3-phenyl-2,5-dihydro-1,2,4-oxadiazol-5-yl)acetamide (39-II). (**39-I**:**39-II** = 77:13): 92% global yield, mp 129–133 °C, from ethyl acetate. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.67; H, 5.39; N, 20.56. IR (KBr): ν_{max} 3444, 3410 br, 1642 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.62 (1H, dd, J = 6.0, 15.3 Hz, **39-I** H-a), 2.89 (1H, dd, J = 5.9, 15.8 Hz, **39-II** H-a), 2.69 (1H, dd, J = 5.5, 15.3 Hz, **39-I** H-b), 2.98 (1H, dd, J = 5.9, 15.8 Hz, **39-II** H-b), 5.96 (1H, m, **39-I** H-5), 5.97 (1H, m, **39-II** H-5), 7.33–7.63 (3H, m, phenyl H), 7.67 (2H, br s, **39-I** N-H, D_2O-exchangeable), 7.74 (2H, br s, **39-II**, N-H, D_2O-exchangeable), 7.78–7.86 (2H, m, phenyl H). ^{13}C NMR (DMSO-d_6): δ 39.68 (**39-I** methylene C), 41.82 (**39-II** methylene C), 87.95 (**39-I** oxad. C-5), 99.97 (**39-II** oxad. C-5), 127.86, 127.92, 128.06, 128.45, 129.44, 130.23, 130.99, (phenyl C), 162.32 (**39-I** oxad.C-3), 164.56 (**39-II** oxad. C-3), 167.47 (formyl C). MS (EI): *m/z* 205, (M^+).

Transformation of 10 and 32 into 13 and 33

A sample of **10** or **32** (0.5 mmol), allowed to stand in solution of CH_3OH (5 mL) in the presence of air and light at rt, quantitatively isomerize within two days into **13** or **33**, which were identified by comparison of their mps, IR, ^1H NMR spectrum with those of authentical samples.

Conversion of 4 and 16 into 5 and 17

Upon standing in solution of CH_3OH in the presence of air and light at room temperature, cycloadducts (**4**) or (**16**) quantitatively degrade within two days into benzonitrile and pyrimidone (**5**)[14] or pyrimidindione (**17**)[32] which were separated by CEPTLC and then identified by comparison of their mps, IR, ^1H NMR spectrum with those of authentical samples.

General procedure for the formation of perchlorates (29) and (35) from 24 and 30

After addition of 70% $HClO_4$ (10 mL) to a stirred solution of oximes (**24**) and (**30**) (1 mmol) in $CHCl_3$ (10 mL), a vigorous stirring was maintained for other 2 h and then the $HClO_4$ phase was separated and allowed to stand overnight in an ice bath. From inorganic solution, isoxazolopyrimidinium perchlorates separated as yellow powders which were recrystallized from acetic acid.

3-Phenyl[1,2,4]oxadiazolo[4,5-*a*]pyrimidin-4-ium perchlorate (29). 89% yield, mp 208–210 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_8N_3O_5Cl$: C, 44.39; H, 2.71; N, 14.12. Found: C, 44.26; H, 2,71; N, 14.10. ^{1}H NMR (DMSO-d_6): δ 7.74 (1H, dd, J = 5.8, 7.8 Hz, H-6), 7.68–7.89 (m, 3H, phenyl H), 7.92–7.98 (m, 2H, phenyl H), 8.98 (1H, dd, J = 1.2, 7.8 Hz, H-5), 9.04 (1H, dd, J = 1.2, 5.8 Hz, H-7). ^{13}C NMR (DMSO-d_6): δ 115.09 (C-6), 126.82, 129.35, 130.96, 132.41 (phenyl C), 156.80 (C-5), 159.22 (C 7), 159.63 (C-3), 164.26 (C-7a). MS (EI): *m/z* 297, (M^+).

3-Phenyl[1,2,4]oxadiazolo[4,5-*c*]pyrimidin-4-ium perchlorate (35). 84% yield, mp 202–204 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_8N_3O_5Cl$: C, 44.39; H, 2.71; N, 14.12 Found: C, 44.48; H, 2,70; N, 14.13. ^{1}H NMR (DMSO-d_6): δ 7.71 (1H, dd, J = 7.6 Hz, H-8), 7.67–7.82 (m, 3H, phenyl H), 7.92–7.98 (m, 2H, phenyl H), 9.01 (1H, dd, J = 0.9, 7.6 Hz, H-7), 9.54 (1H, d, J = 0.9 Hz, H-5). ^{13}C NMR (DMSO-d_6): δ 106.43 (C-8), 125.33, 129.75, 132.47, 134.12 (phenyl C), 154.13 (C-3), 160.17 (C-7), 164.21 (C-5), 164.77 (C-8a). MS (EI): *m/z* 297, (M^+).

General procedure for the Beckmann rearrangement of *Z*-oximes (7), (13), (26), and (33) into 8, 14, 27, and 34

To a stirred ice-cooled solution of oximes (**7**), (**13**), (**26**), and (**33**) (1.0 mmol) in dry dioxane (15 mL) was added, droopwise, $SOCl_2$ (0.50 mL, 6.6 mmol) over a period of 10 min and then the reaction mixture was allowed to reach the rt. After having stirred for 10 h, the reaction mixture was poured into cold water (50 mL) and extracted with EtOAc (2 × 30 mL). The organic layers were combined and washed with water (2 × 30 mL), dried with anhydrous Na_2SO_4 and evaporated under vacuum. Flash chromatography of the residue afforded amides (**8**), (**14**), (**27**), and (**34**).

2-Methoxy-*N*-phenylpyrimidine-5-carboxamide (8). 62% yield, mp 199–201 °C, from ethyl acetate. Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 61.67; H, 4.86; N, 18.36. IR (KBr): ν_{max} 3340 br, 1664 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.89 (3H, s, methoxyl H), 7.02–7.35 (3H, m, phenyl H), 7.62–7.87 (2H, m, phenyl H), 8.75 (1H, br s, amide N-H, D_2O-exchangeable), 9.14 (2H, s, H-4 and H-6). ^{13}C NMR (DMSO-d_6): δ 54.42 (methoxyl C), 119.54 (C-5), 123.48, 124.32, 128.81, 138.90 (phenyl C), 159.59 (C-4, C-6), 165.37 (amide C); 170.30 (C-2). MS (EI): *m/z* 229, (M^+).

4-Methoxy-2-oxo-*N*-phenyl-1,2-dihydropyrimidine-5-carboxamide (14). 61% yield, mp 218–220 °C, from ethyl acetate. Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.90; H, 4.50; N, 17.26. IR (KBr): ν_{max} 3344 br, 1666, 1628 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.99 (3H, s, methoxyl H),

7.06–7.49 (3H, m, phenyl H), 7.64–7.78 (2H, m, phenyl H), 9.4 (1H, d, *J* = 5.4 Hz, H-6), 11.73 (1H, bd, N-H, D_2O-exchangeable), 9.85 (1H, br s, amide N-H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 53.92 (methoxyl C), 104.72 (C-5), 121.87, 123.59, 129.42, 138.80 (phenyl C), 158.10 (C-6), 158.74 (C-4), 164.41 (C-2), 164.33 (amide C). MS (EI): *m/z* 245, (M^+).

2,4-Dioxo-*N*-phenyl-3,4-dihydropyrimidine-1(2*H*)-carboxamide (27). 66% yield, mp 238–240 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.03; H, 3.92; N, 18.22. IR (KBr): ν_{max} 3328 br, 1678, 1668, 1644 cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.01 (1H, d, *J* = 7.6 Hz, H-5), 7.01–7.28 (3H, m, phenyl H), 7.48–7.66 (2H, m, phenyl H), 8.55 (1H, d, *J* = 7.6 Hz, H-6), 11.21 (1H, br d, N-H, D_2O-exchangeable), 8.7 (1H, br s, amide N-H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 100.82 (C-5), 119.69, 123.28, 128.75, 138.80 (phenyl C), 148.54(C-6), 159.25 (C-2), 162.27 (amide C), 162.91 (C-4). MS (EI): *m/z* 231, (M^+).

6-Oxo-*N*-phenyl-1,6-dihydropyrimidine-5-carboxamide (34). 62% yield, mp 224–226 °C, from ethyl acetate. Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.19; H, 4.28; N, 19.47. IR (KBr): ν_{max} 3346 br, 1680, 1636 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.05–7.19 (3H, m, phenyl H), 7.61–7.78 (2H, m, phenyl H), 8.33 (1H, s, H-6), 7.87 (1H, d, *J* = 9.2 Hz, H-2), 9.69 (1H, br s, amide N-H, D_2O-exchangeable), 10.45 (1H, br d, N_3-H, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 118.38 (C-5), 118.35, 124.23, 128.96, 139.44 (phenyl C), 152.43 (C-6), 160.19 (C-2), 162.21 (C-4), 164.11 (amide C). MS (EI): *m/z* 215, (M^+).

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