Pergamon

Tetrahedron Vol. 51, No. 43, pp. 11855-11862, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00746-6

Reaction of Diazines and their Benzo derivatives with Benzonitrile oxide

Giovanni Grassi,* Francesco Risitano and Francesco Foti

Istituto di Chimica dei Composti eterociclici, Università, Vill. S. Agata 98166 Messina , Italy

Abstract: The reaction of diazines 1 and benzodiazines 2 with benzonitrile oxide in refluxing benzene affords regio, site and stereospecific cycloadducts to the diazine ring and/or products derived from them.

Introduction

In recent years the involvement of heterocycles in cycloaddition reactions has received considerable attention.[1] These have found especial application in Diels-Alder reactions where they may come into play either as 4π or 2π components to give annelated 6-membered rings. In connection with this, opportunely substituted diazines have been found to function positively as azadienes in inverse electron demand Diels-Alder reactions with electron-rich dienophiles.[2] Moreover, dipolar 1,3-cycloaddition reactions where the heterocycle acts as a 2π component have been little studied. The only reactions of this type described are those regarding the cycloaddition of diazoalkanes to variously substituted pyridazines[3] and of nitrilimines to aminopyrazine,[4] where the dipoles are shown to be regioselectively added to a C=C double bond to give pyrazolo-fused systems in both cases.

This study, as part of our interest in the behaviour of nitriloxides towards O,N-[5] and N-heterocycles,[6] details the results obtained with diazines **1** and their benzoderivatives **2**. In particular these dipolarophiles, which contain C=C and C=N double bonds have been found to undergo initial nitriloxide cycloaddition to the C=N rather than to the olefinic bond.

Results and Discussion

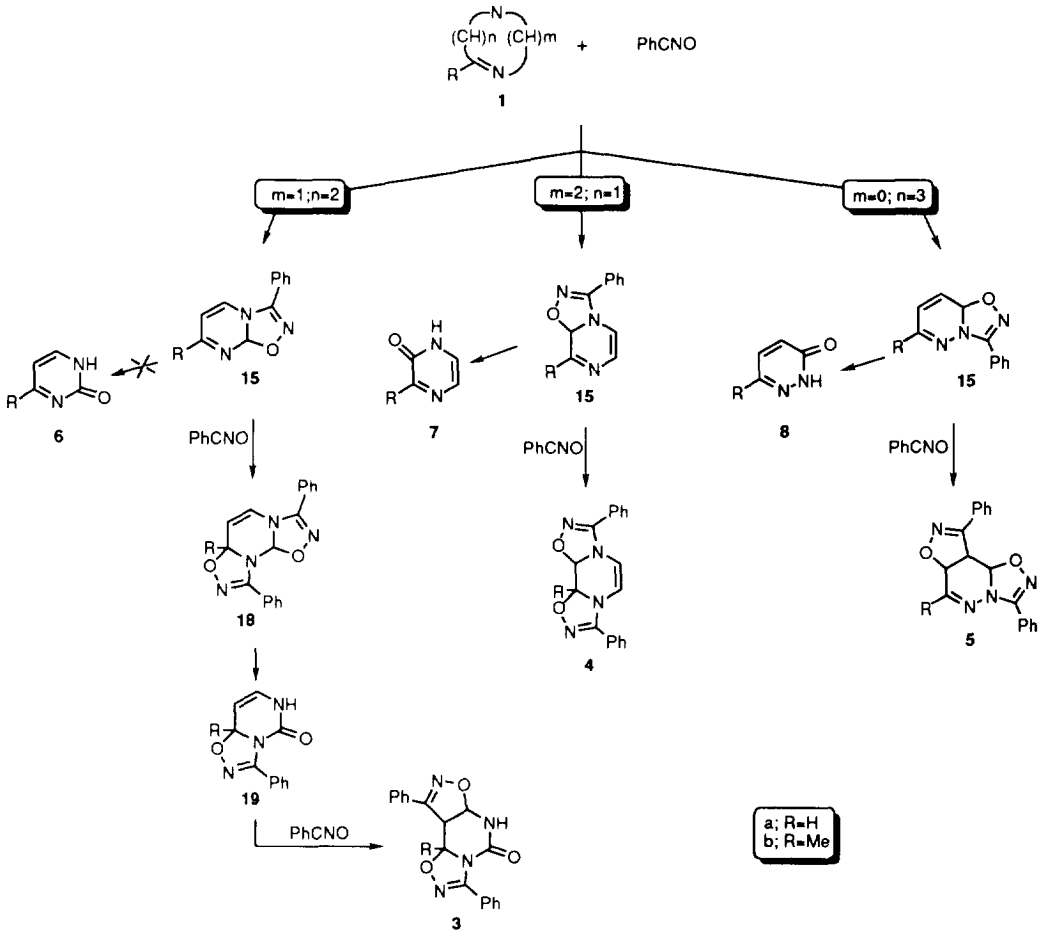
Cycloaddition Products of benzonitrile oxide to diazines **1** (Scheme 1). - Pyrimidines (**1**; m=1, n=2) react with benzonitrile oxide[7] (BNO) in refluxing benzene in a 1:3 molar ratio, to give the tetrahydropyrimidin-2-ones **3**.

The reactions of pyrazines (**1**; m=2, n=1) and pyridazines (**1**; m=0, n=3) respectively yielded the tetrahydropyrazines **4** and the tetrahydropyridazines **5** as the major products; diazinones **7** and **8** were also isolated but in lower yields, below 4%. The structures of the latter compounds were assigned by comparison with

known samples.[8] Great quantities of 3,4-diphenylfuroxan **17** were isolated in all reactions, while the other BNO dimer - 3,6-diphenyl-1,4,2,5-dioxadiazine **16**[9] (Scheme 3) - was never detected.

The non-optimized yields of biscycloadducts **3**, **4** and **5** are shown in the Table; their structure was assigned on the basis of analytical and spectroscopic data and confirmed by an X-ray crystallographic analysis carried out on **3b** and **5a**.[10]

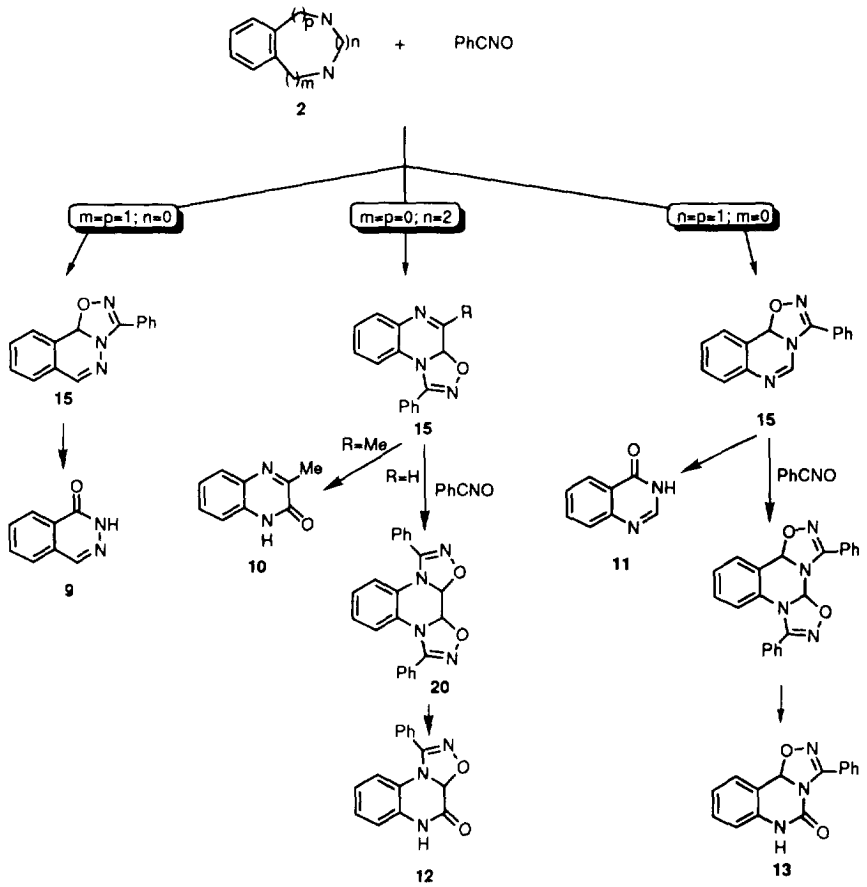
In consideration, therefore, of the fact that under our reaction conditions (see Experimental) only the above-mentioned products are obtained, these reactions seem to be regio, site and stereospecific, although a mixture of regio and site isomeric cycloadducts might reasonably have been expected on the basis of a simple inspection of the structure of the diazines started out with.



SCHEME 1

Cycloaddition Products of benzonitrile oxide to benzodiazines **2**. (Scheme 2) - BNO reacts with the benzodiazines **2** exclusively at the C=N bond of the heterocyclic ring, but the corresponding mono and bisadducts were found to undergo complete conversion to benzodiazinones **9**, **10**, **11**, **12** and **13**, which are the only products isolated under our conditions along with 3,4-diphenylfuroxan **17**.

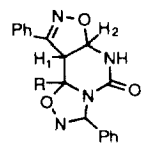
The yields of the above products are shown in the experimental section. The structures of compounds **9**, **10** and **11** were assigned by comparison with authentic samples.[11] The structures of cycloadducts **12** and **13**, assigned on the basis of analytical and spectroscopic data, were confirmed by hydrolytic scission to the known 2,3-dihydroxyquinoxaline[12] and 2,4-dihydroxyquinazoline,[13] respectively.



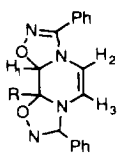
SCHEME 2

The results obtained show how diazines **1** and **2** possess an unusual dipolarophilic activity towards the BNO, as already observed for pyridine and its benzoderivatives quinoline and isoquinoline;[14] unlike these, however, under the same reaction conditions abnormal dimerization of BNO to 1,4,2,5-dioxadiazine **16** does not occur. This excludes the intermediacy of the zwitterion **14** (Scheme 3, path i) and hence a two-step cycloaddition, as found with pyridine and nitrile oxide.[15] Thus, in accordance with previous experiences on 1,3-dipolar cycloadditions,[16] the preferred route for the formation of our compounds is that of Scheme 3 path ii.

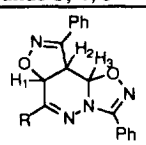
Table. Analytical and Spectral Data of Compounds **3, 4, 5**



3



4



5

Compd.	Yield %	Mp(°C)	Formula	Analysis % Calcd./Found C	H	N	Ir,ν (cm^{-1})	^{1}H-nmr Spectra (δ)[a] H_1	R	H_2	H_3	NH
3 a	25	235	$C_{18}H_{14}N_4O_3$	64.65	4.22	16.76	1735	3.74t	5.80d	5.87dd		6.15d
				64.51	4.24	16.88	3260	(7.2)	(7.2)	(7.2, 4.6)		(4.6)
3 b	27	245	$C_{19}H_{16}N_4O_3$	65.49	4.63	16.09	1728	3.84d	1.50s	5.71dd		6.02d
				65.73	4.71	16.02	3298	(7.7)		(7.7,4.2)		(4.2)
4 a	25	169	$C_{18}H_{14}N_4O_2$	67.92	4.43	17.60	1598	5.43s		6.03s		
				67.75	4.41	17.72	1563					
4 b	22	164	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86	1601	5.52s	1.51s	5.98s		
				68.86	4.94	16.73	1568					
5 a	29	161	$C_{18}H_{14}N_4O_2$	67.92	4.43	17.60		4.81dd	b	3.79t	5.10d	
				67.72	4.38	17.76		(9.2, 2.8)		(9.2)	(9.2)	
5 b	24	147	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86		4.77d	2.32s	3.95t	5.01d	
				68.81	4.90	16.72		(9.6)		(9.6)	(9.6)	

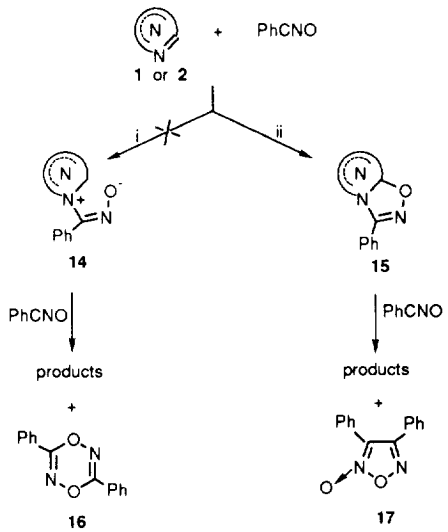
[a]Obtained in $CDCl_3$ at 60 MHz and at 80 MHz. The coupling constants (Hz) are given in parentheses.
[b]Overlapped by aromatic protons.

In perfect analogy with what happens for α,β-unsaturated imines and nitrile oxides,[17] where the dipole reacts only at the most polar C=N bond leaving the C=C bond intact, the first attack of BNO on diazines **1** or **2** always leads to the specific formation of the non-isolated cycloadducts **15**.

In cycloadditions to methyldiazines **1b** the steric preference for the dipole attack on the unsubstituted C=N bond is demonstrated by the fact that the known methyldiazinones **7b** and **8b** are obtained. The corresponding monoadducts **15** cannot be isolated but, as is known for particularly strained dipolarophiles,[18] their dipolarophilic reactivity is greater than that of the diazines started out with. These therefore undergo the attack of a second BNO molecule at one of the reactive sites incorporated in them, which seems, this time, to depend on the reciprocal position of the two nitrogen atoms in the starting bases.

Certainly the addition of BNO to pyridazines **1** (m=0, n=3) (Scheme 1), as mentioned, initially supplies monocycloadduct **15** which either degrades to a very small extent into the known pyridazones **8** or reacts further

with the dipole still in solution. In comparison with the first cycloaddition, the site-selectivity of this second attack is reversed. The dipole is added regiospecifically only to the C=C of **15** generating the isoxazolinic ring found in compound **5** rather than the expected second oxadiazolinic ring. This increased dipolarophilic activity of the olefinic bond can be correlated with the grater steric impediment of the C=N when close to annelation. In confirmation of this result, additon to phthalazine **2** (m=p=1, n=0) (Scheme 2) leads to benzodiazinone **9** where a C=N double bond remains unaltered. The observed stereospecificity is consistent with the addition of the dipole to the less sterically hindered face of the C=C double bond.[18]



SCHEME 3

With pyrimidines **1** (m=1, n=2) and pyrazines **1** (m=2, n=1) (Scheme 1) the reaction with BNO usually occurs after oxadiazolinic bisadducts **18** and **4** respectively have been obtained as a result of the favoured anti attack of the dipole on the two C=N of every single molecule. Nevertheless, in the case of pyrimidines, the reaction does not stop at this stage, but is complicated by a process of rearrangement not observed in the other diazines. Indeed, it was impossible either to isolate or identify in solution the expected product of biscycloaddition **18** since it seems somewhat unstable due to the presence in its molecule of an oxadiazolinic ring where a CH is bonded to three heteroatoms. In accordance with a known process[19] it tends to decompose after elimination of benzonitrile and the subsequent formation of annelated pyrimidone **19**. This contains a highly reactive enamminic system which reacts spontaneously with the BNO still present in solution yielding regioisomer **3** exclusively.[15] The alternative route to **3** through the double cycloaddition of the dipole to the azadienic system of the pyrimidones **6**,[8] which ought to have been achieved in the same way as for the previous similar reactions from mono cycloadduct **15**, has to be excluded for two reasons:

a) a trial in which BNO was added directly to the known pyrimidinone **6a** failed to yield the corresponding product **3a**;

b) similar annelated diazinones have never been isolated in BNO reactions either with pyridazine **1** (m=0, n=3) or with pyrazine **1** (m=2, n=1) (Scheme 1), despite the fact that the diazinones **7** and **8** started out with are formed normally during the above reactions.

Similar progress might be expected for the obtainment of annelated **13** from BNO and quinazoline **2** (m=0, n=p=1). Thus the addition of BNO to quinoxalines **2** (m=p=0,n=2) confirms the results obtained with the corresponding monodiazines **1** (m=2, n=1). In fact, in the latter reaction bis **20** or monoadducts **15** must have been formed even though they cannot be isolated; and in their place annelated benzodiazinone **12** and methylbenzodiazinone **10** respectively were obtained. Their obtainment, even in consideration of the fact that pyrazine **1b** gives rise to the bisadduct **4** by cycloaddition of the BNO to the two C=N double bonds regardless of R, confirms that the annelated diazinones produced are subsequent to the formation of the biscycloadducts.

Experimental

IR spectra were performed on a Perkin Elmer 682 spectrometer and microanalyses on a Carlo Erba EA 1102 element analyser. Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded in the solvent indicated on a Hitachi-Perkin-Elmer R 24A (60 MHz) and on a Bruker 80 Q instrument, using tetramethylsilane as internal reference. Column chromatography was performed on Merck silica gel 60.

Reactions of the diazines 1 and 2 with BNO: General procedure.

A solution of diazine **1** or **2** (5 mmol) and benzonitrile oxide[7] (15 mmol) in benzene (150 ml) was refluxed for 3 h. After evaporation of the solvent, the mixture was chromatographed on a column of silica gel with chloroform as eluant. Diphenylfuroxan **17** was eluted first, followed by the products below described. The yields are given in Table except where otherwise noted.

*Pyrimidine **1a** (m=1, n=2) and BNO:*

3a,4a,9a,9b-tetrahydro-1,7-diphenylisoxazolo[5,4-d][1,2,4]oxadiazolo[4,5-c]pyrimidin-5-one **3a**.

*4-Methylpyrimidine **1b** (m=1, n=2) and BNO:*

3a,4a,9a,9b-tetrahydro-1,7-diphenyl-9a-methylisoxazolo[5,4-d][1,2,4]oxadiazolo[4,5-c]pyrimidin-5-one **3b**.

*Pyrazine **1a** (m=2, n=1) and BNO:*

Pyrazin-2-one **7a** (4 %), m.p.185-187°C (lit,[8a] 187-188°C);

10a,10b-dihydro-3,8-diphenyl-1,2,4-dioxadiazolo[4,5-a][4,5-c]pyrazine **4a**.

*2-Methylpyrazine **1b** (m=2, n=1) and BNO:*

3-Methylpyrazin-2-one **7b** (3 %), m.p.138-139°C (lit,[8b] 140-142°C);

10a,10b-dihydro-3,8-diphenyl-10a-methyl-1,2,4-dioxadiazolo[4,5-a][4,5-c]pyrazine **4b**.

*Pyridazine **1a** (m=0, n=3) and BNO:*

Pyridazin-3-one **8a** (3 %), m.p. 105-107°C (lit,[8c] 103-104°C);

6a,9a,9b-trihydro-3,9-diphenylisoxazolo[4,5-d][1,2,4]oxadiazolo[4,5-b]pyridazine **5a**.

*3-Methylpyridazine**1b** (m=0, n=3) and BNO:*

3-Methylpyridazin-6-one **8b** (3 %), m.p. 140-142°C (lit,[8d] 143°C);

6a,9a,9b-trihydro-3,9-diphenyl-6-methylisoxazolo[4,5-d][1,2,4]oxadiazolo[4,5-b]pyridazine **5b**.

Phthalazine 2 (m=p=1;n=0) and BNO:

Phthalazin-1-one **9** (45%), m.p.187-188°C (lit,[11a] 182°C);

Quinoxaline 2 (m=p=0;n=2) and BNO:

3aH-1-phenyl-1,2,4-oxadiazolo[5,4-c]quinoxalin-4-one **12** (35%), m.p.271-273°(from methanol) (Found: C, 68.01; H, 4.07; N, 15.74. $C_{15}H_{11}N_3O_2$ requires C, 67.91; H, 4.18; N, 15.84 %); $\nu_{C=O}$ 1705 cm^{-1}; δ_H [$(CD_3)_2CO$] 6.55 (1H,s); 7.30-8.11 (9H,m); 12,2 (NH).

*2-Methylquinoxaline **2** (m=p=0;n=2) (R=Me) and BNO:*

3-Methylquinoxalin-2-one **10** (37 %), m.p.242-243°C (lit,[11c] 246-248°C);

Quinazoline 2 (n=p=1;m=0) and BNO:

10bH-3-phenyl-1,2,4-oxadiazolo[4,5-c]quinazolin-5-one **13** (30%), m.p.320-321°(from methanol) (Found: C, 68.10; H, 4.11; N, 15.69. $C_{15}H_{11}N_3O_2$ requires C, 67.91; H, 4.18; N, 15.84 %); $\nu_{C=O}$ 1700 cm^{-1}; δ_H [$(CD_3)_2CO$] 6.45 (1H,s); 7.09-7.90 (9H,m); 10,52 (NH);

Quinazolin-4-one **11** (16%) m.p.212-214°C (lit,[11b] 216-219°C).

References

1 Katritzky, A. R.; Dennis, N. *Chem. Rev.*, **1989**, *89*, 827, and references therein.

2 Boger, D. L. *Tetrahedron*, **1983**, *39*, 2869; Boger, D. L. *Chem. Rev.*, **1986**, *86*, 781.

3 Stanovnik, B. *Tetrahedron*, **1991**, *47*, 2925.

4 Elgemeie, G. E. H.; Elfahham, H. A.; Ghozlan, S. A. S.; Elnagdi, M. H. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 1650.

5 Risitano, F.; Grassi, G.; Foti, F.; Caruso F.; Lo Vecchio, G. *J. Chem. Soc. Perkin I* , **1979**, 1522.

6 Grassi, G.; Foti, F.; Risitano, F.; Bruno, G.; Nicolò F.; De Munno, G. *J. Chem. Soc. Perkin I* , **1993**, 2615.

7 Both generated *in situ* from benzohydroxamoyl chloride and triethylamine and prepared separately (A. Quilico and G. Speroni, *Gazz. Chim. Ital.*, **1946**, *76*, 148.

8 (a) Weijlard, J.; Tishler, M.; Erickson, A.E. *J. Am. Chem. Soc.*, **1945**, *67*, 802; (b) Jones, R.G. *J. Am. Chem. Soc.*, **1949**, *71*, 78; (c) Gabriel, S. *Chem. Ber.*, **1909**, *42*, 657; (d) Poppenberg, O. *Chem. Ber.*, **1901**, *34*, 3263.

9 De Sarlo, F. ; Guarna, A. *J. Chem. Soc., Perkin Trans.*, **1976**, *2*, 626.

10 Grassi, G.; Risitano, F.; Foti, F.; Bruno, G. submitted for publication in *J. Chem. Research* .

11 (a) Gabriel S.; Neumann, A. *Chem. Ber.*, **1893**, *26*, 523; (b) Gabriel S.; Posner, T. *Chem. Ber.*, **1895**, *28*, 1035; (c) Leese C. L.; Rydon, H. N. *Chem. Soc.*,**1955**, 308.

12 Hinsberg, O. *Chem. Ber.*, **1908**, *41*, 2037.

13 Culbertson, H.; Decius, J.C.; Christensen, B.E. *J. Am. Chem. Soc.*, **1952**, *74*, 4834.

14 Corsaro, A.; Perrini, G.; Caramella, P.; Marinone Albini F.; Bandiera, T. *Tetrahedron Letters*, **1986**, *27*, 1517.

15 Caramella, P.; Bandiera, T.; Marinone Albini, F.; Gamba, A.; Corsaro A.; Perrini, G. *Tetrahedron Letters*, **1988**, *44*, 4917.

16 Caramella, P.; Grunanger, P. in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley Interscience, New York, **1984**, *1*, 291, and references therein.

17 Singh, N.; Sandhu, J.S.; Mohan, S. *Tetrahedron Letters*, **1968**, 4453.

18 Stajer, G.; Bernarth, G.; Szabo, A.E.; Sohar, P.; Argay, G.; Kalman, A. *Tetrahedron* , **1987**, *43*, 5461, and references therein.

19 Srimannarayana, G.; Srivastava, R.M.; Clapp, L.B. *J. Heterocycl. Chem.*, **1970**, *7*, 151.

(*Received in UK* 28 *July* 1995; *revised* 1 *September* 1995; *accepted* 8 *September* 1995)