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CYCLOADDUCTS OF BENZONITRILE OXIDE TO PYRIDINE. A CASE OF A TWO-STEP CYCLOADDITION[1,☆]

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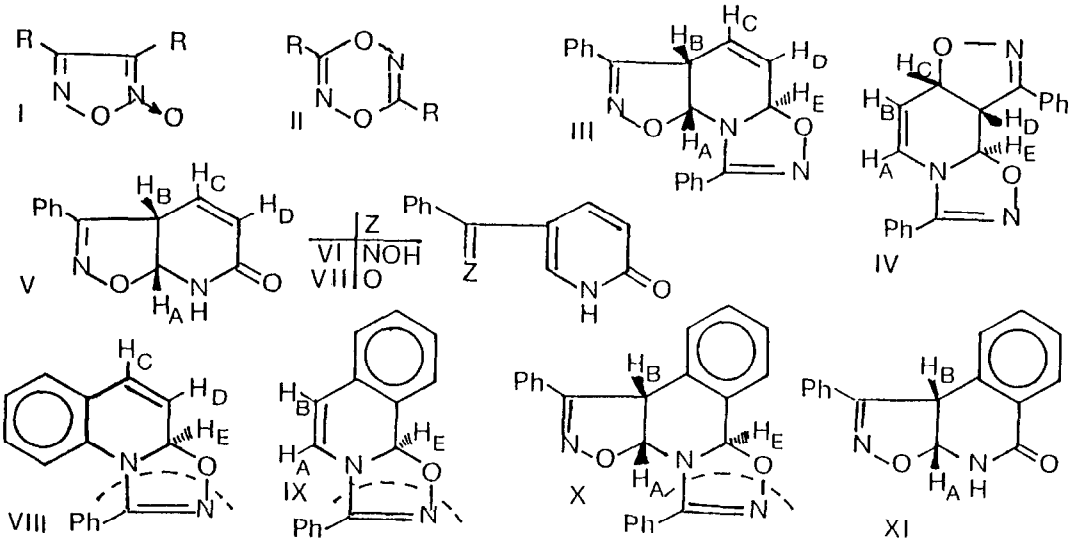
Abstract: Pyridine adds benzonitrile oxide in apolar solvents, affording fair yields of bisadducts III and IV. Quinoline and isoquinoline afford isolable monocycloadducts VIII and IX.

Pyridine displays a marked catalytic activity in most nucleophilic reactions of carboxylic acid derivatives[2]. De Sarlo and Guarna have reported a neat case of pyridine catalysis with nitrile oxides[3]. While these dipoles usually dimerize to furoxanes I, pyridine induces the formation of the 1,4,2,5-dioxadiazine dimers II. The yields of the dimers II are quantitative for reactions performed in ethanol, but drop remarkably when apolar solvents were used.

We found that in apolar solvents the 2:1 cycloadducts III and IV were also formed in fair yields. Thus, generation of benzonitrile oxide (BNO) from benzhydroximoyl chloride and triethylamine (1 equiv) in diethyl ether at 0° in the presence of pyridine (5 equivs) afforded bisadduct III, m.p. 173-4°C, which crystallized out in 26% yield, along with triethylamine hydrochloride. Column chromatography of the mother liquors gave bisadduct IV, m.p. 133-4°C, in 9% yield, along with dimers I and II.

The structures of the cycloadducts rely upon spectroscopic and chemical evidence. The NMR spectrum of the major adduct III shows a broad double doublet (J=9.5; 4.0 Hz) at 4.16 δ, which can be attributed to a somewhat deshielded 4-isoxazolinic proton[4]. The signals of the other four non-aromatic protons fall together in a complex multiplet at 6-6.4 δ, and could be simplified by addition of Eu(fod)$_3$. The extrapolated δs, the ΔM values and the coupling constants deduced from decoupling experiments in the presence of the shift reagent are given in the Table. The sequence of couplings fully supports structure III. The multiplicity of the 4-isoxazolinic H_B arises because of the vicinal couplings with the 5-isoxazolinic H_A, which appears as a neat doublet (J=9.5 Hz), and with a vinylic H_C (J=4 Hz). The protons adjacent to nitrogen - the 5-isoxazolinic and the oxadiazolinic protons - are the most shifted downfield by Eu(fod)$_3$ and the different ΔMs may suggest an anti relationship of the two five membered rings fused to pyridine. An <u>anti</u> stereochemistry[5] is usually observed in cycloadditions of nitrile oxides to conformationally mobile systems. Confirmation of structure III was provided by degradation. The oxadiazoline N-O bond can be cleaved rather easily[6]. Upon boiling 3 h in CCl_4 in the presence of azoisobutyronitrile, adduct III fragments to the dihydropyridone V, m.p. 160-1°C. Acidic hydrolysis of V in EtOH/HCl afforded (Δ 10') pyridone oxime VI[7], m.p. 214-6°C and then (Δ 3 h) ketone VII, m.p. 193-5°C, identical with an authentic specimen[7].



The NMR signals of the five protons of the pyridine ring of the minor bisadduct are well separated (Table) and are consistent with structure IV. The 4-isoxazolinic H_D is a triplet at 3.50 δ (J=8 Hz). It is shielded by 0.66 ppm with respect to the analogous proton of III and its high field location is typical for isoxazolines carrying a 4-substituent with only slight deshielding ability, i.e. alkyls or sp^3 carbons. H_D is coupled with a dd at 4.91 δ and with a d at 5.51 δ, which can be attributed to the 5-isoxazolinic H_C and oxadiazolinic H_E, resp.[8] The stereochemistry of the bisadduct is anti, as suggested by the large coupling constant (8 Hz) through the bond connecting the two five-membered heterocyclic rings.

Under similar conditions, quinoline and isoquinoline add BNO to yield monocycloadducts VIII, oil, and IX, m.p. 92-3°C, resp., which could be isolated in fair yields (40-60%) by flash column chromatography. In reactions with isoquinoline, bisadduct X, m.p. 191-2°C, was

TABLE - NMR data of cycloadducts in $CDCl_3$ (TMS i.s.)[a]

Comp.		A	B	C	D	E	J_{AB}	J_{BC}	J_{CD}	J_{DE}
III	δ	6.08 d	4.16 dd[b]	6.08 dd[b]	6.38 dd[b]	6.14 d[b]	9.5	4.0	11.0	1.0
	ΔM	2.24	1.28	0.84	1.12	3.12				
IV	δ	6.80 d	5.45 dd	4.91 dd	3.50 t	5.51 d	7.0	5.2	8.0	8.0
V	δ	5.95 d	4.47 o[c]	6.43 dd	6.06 o[c]		9.0	3.0	10.0	
VIII	δ			--[d]	6.08 dd	6.33 d			10.0	3.0
IX	δ	6.51 d	5.79 d			6.76 s	8.0			
X	δ	6.09 d	4.89 d			6.55 s	8.0			
XI	δ	6.12 dd[e]	4.85 d				7.8			

a) labels of protons are shown in formulas; b) broadened because of allylic and homoallylic couplings, $J_{BC}=J_{BD}=J_{CE}\sim 1$ Hz; c) the signals are octets because of an allylic coupling, $J_{BD}=2.0$ Hz d) occurs under aromatic signals; e) $J_{NH,A}=4.0$ Hz.

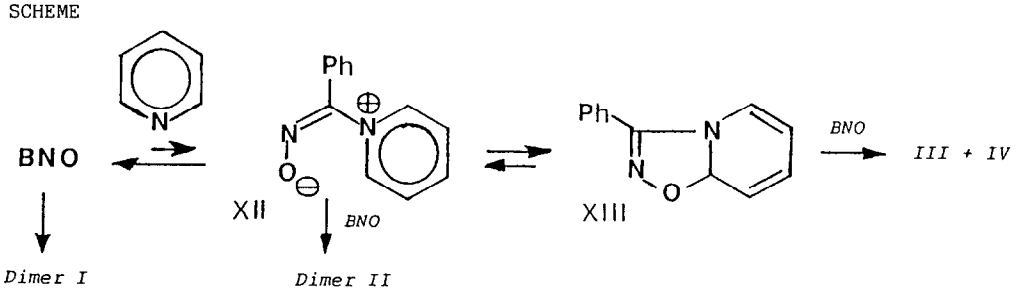
also isolated. Polar solvents (EtOH) do not change remarkably the product distribution of these reactions and only in the reaction of quinoline in EtOH some dioxadiazine dimer (10-20%) was detected. The adducts VIII, IX and X are more fragile than the bisadducts of pyridine. Upon standing in solvents a few days at r.t., in the presence of air, the adducts fragment with formal loss of benzonitrile (dashed lines) and formation of carboxamides, i.e. carbostyril, isocarbostyril and amide XI, resp.[9] Interestingly, the quinoline adduct VIII slowly reverts to reactants. A solution of VIII and excess norbornene in benzene, when kept 2 weeks under nitrogen, affords the BNO adduct to norbornene, along with quinoline.

The reactions discussed above are quite unusual. The three heteroaromatic bases display an unexpectedly high dipolarophilic activity towards BNO and their cycloadditions are accompanied by variable amounts of the abnormal dimer II. The results can be accomodated within a single reaction scheme (see Scheme), which rests upon the similar basicity[10] of the three heteroaromatic bases. Reversible addition of these tertiary bases to the moderately electrophilic BNO affords zwitterion XII in a low stationary concentration[11]. Aside from reversion to reactants, XII can enter the dimerization route or undergo an electrocyclic closure to monocycloadduct XIII.

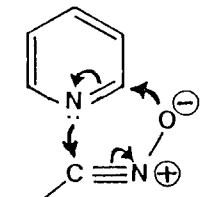
In the case of quinoline and isoquinoline, cyclization is favoured both in apolar and polar solvents, because of the moderate, fractional, loss of aromaticity with these bicyclic heteroaromatics[12]. The monocycloadducts are isolable and only the quinoline adduct shows a weak inclination to cycloreversion. In the case of pyridine the loss of aromaticity is unavoidably larger and so the cost of cyclization and the energy of the cycloadduct XIII increase as well. The latter should be higher in energy than the reactants and unstable to cycloreversion, as suggested by a comparison with the behaviour of the quinoline adduct. Although XIII is expected to occur only in a low stationary concentration, it contains a highly reactive dienamine moiety and can be trapped by BNO[13]. In apolar solvents cyclization and trapping compete with the normal and abnormal dimerization. In polar solvents the stability of the zwitterion is remarkably enhanced and only the dimerization to dioxadiazines is observed.

The Scheme is based on the formation of a zwitterion and accounts well for the products and the remarkable solvent effects observed. Cycloadducts are viewed as secondary products, which derive from the zwitterion in a subsequent electrocyclic closure. The scheme implies then a rare[14] case of a two-step cycloaddition. Conceivably the monocycloadducts could be linked directly to the reactants through a concerted one-step cycloaddition. A conventional $\pi^4_s + \pi^2_s$ concerted cycloaddition involving only the π^2_s electrons of pyridine is however rather unlikely, since the attendant loss of aromaticity should increase the energy of the transition

SCHEME



state prohibitively[7]. A conceivable alternative, shown in XIV, makes use of the pyridine lone pair, just as in zwitterion formation. All centers of the forming ring are interacting but the 8 (not 6) electrons involved ar not cyclically delocalized, since the n an π orbitals at the pyridine nitrogen are orthogonal. This reaction mode belongs to the pseudopericyclic variety, like hydroboration[15]. It is neither allowed nor forbidden, and is stabilized only by an acyclic delocalization of the allylic type, as in the isoconjugate heptatrienate anion. No overwhelming energetic advantage of XIV over the formation of the aromatic zwitterion is then expected, especially in polar solvents.



XIV

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☆Dedicated to Professor Rolf Huisgen on his 65th birthday

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