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FRAGMENTATION OF NITRILE OXIDES WITH TRIETHYLAMINE [1]

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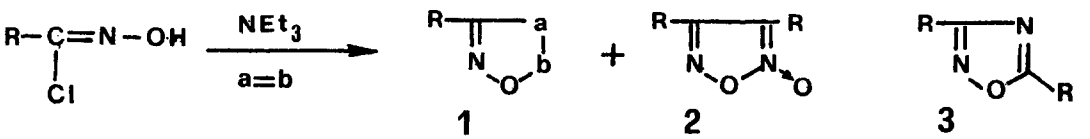
Abstract: The formation of 1,2,4-oxadiazoles is frequently observed as a side reaction in cycloadditions with nitrile oxides generated in situ and follows from a fragmentation induced by Et_3N. This latter is oxidized to N,N-diethylvinylamine, which is trapped as a cycloadduct.

Nitrile oxides are usually generated in situ from suitable precursors. Dehydrohalogenation of the stable and storable hydroximic acid chlorides with triethylamine in an inert solvent is a very efficient entry to nitrile oxides and the procedure has gained general acceptance for cycloaddition purposes[3]. While active dipolarophiles afford very good yields - almost quantitative - of cycloadducts 1, with lower reactive dipolarophiles the normal decay of nitrile oxides, i.e. the dimerization to furoxan 2, competes. In addition, however, noteworthy amounts of 1,2,4-oxadiazole 3 were observed[4].



The origin of 1,2,4-oxadiazoles is puzzling. Formally oxadiazoles 3 derive from 2 moles of nitrile oxide with loss of an oxygen atom. Because of the uncertainity about the mechanism of deoxygenation, however, oxadiazole formation has never been fully discussed and remained almost confined in the experimental part of most papers dealing with nitrile oxide reactions[4,5].

Effect of triethylamine on cycloadditions and dimerization of BNO

Generation in situ of benzonitrile oxide (BNO) in the presence of trans stilbene, a typical dipolarophile of low reactivity[6], affords trans 3,4,5-triphenylisoxazoline, 1 (a=b=CHC_6H_5), 3,4-diphenylfuroxan, 2 and 3,5-diphenyl-1,2,4-oxadiazole, 3. The Table shows the distribution of the products in reactions performed in benzene and methylene chloride with different amounts of triethylamine. The yields of 3,5-diphenyl-1,2,4-oxadiazole 3 depend remarkably upon the excess of triethylamine and on the nature of the solvent as well. Oxadiazole increases with increasing excess of triethylamine, while the cycloadduct and diphenylfuroxan decrease. Sharper changes occur in the more polar methylene chloride.

Table - Yields of trans 3,4,5-triphenylisoxazoline 1, 3,4-diphenylfuroxan 2 and 3,5-diphenyl-1,2,4-oxadiazole 3 in cycloadditions of BNO to stilbene (1.2 equiv)[a]. BNO was generated in situ in the appropriate solvent with the given equiv of triethylamine.

Solvent	NEt_3 equiv	1	2	3
Benzene	1	55	40	1.9 (1.7)[b] (2.0)[c]
	3	52	36	3.7
	6	50	35	4.2
	10	48	33	4.7
Methylene chloride	1	59	24	4
	3	46	19	15
	6	39.5	16	19
	10	30	12	17

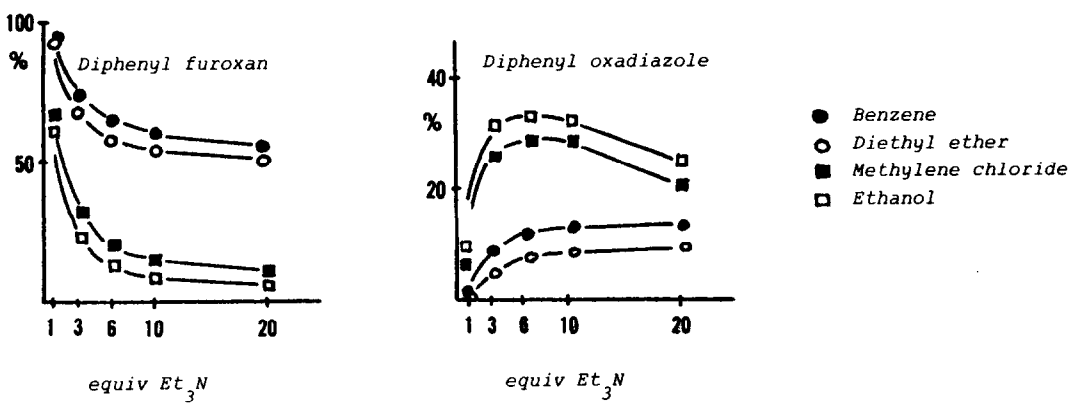
[a]*Gaschromatographic determinations were performed with a column packed with a 3.8% UC W 982 on Supelcoport 80/100 mesh.* [b]*In the presence of added trans 3,4,5-triphenylisoxazoline (1 equiv).* [c]*In the presence of added 3,4-diphenylfuroxan (1 equiv)*

Numbers in parentheses show that the yields of oxadiazole are almost unchanged in reactions performed in the presence of added triphenylisoxazoline or diphenylfuroxan. These experiments exclude a determining role of the cycloaddition to the isoxazolinic or furoxan C=N double bond on the way leading to oxadiazole 3. Cycloadditions to the isoxazolinic C=N bond have been observed in some cases, and afford adducts, which have only a moderate stability and fragment thermally to 1,2,4-oxadiazoles[7].

The trends discussed above show up more clearly when examining the effect of triethylamine upon the dimerization of BNO. The Figure summarizes the dependence of the yields of diphenylfuroxan and oxadiazole on the amount of base used for the in situ generation of BNO. In diethyl ether and benzene, the yields of furoxan drop rather gently, while those of oxadiazole increase at a lower rate. In the more polar solvents, viz. methylene chloride and ethanol, the effects are remarkably magnified.

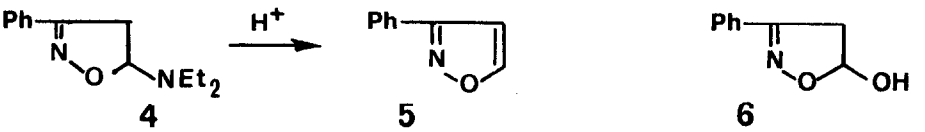
Small amounts of benzonitrile could also be detected. In the runs in methylene chloride with 10, 20 and 50 equiv Et_3N a 2, 3 and 5%, resp., yield of benzonitrile was determined by glc.

Figure. Influence of equiv Et_3N in the in situ generation of BNO



Formation of 3-phenyl-5-diethylamino-2-isoxazoline

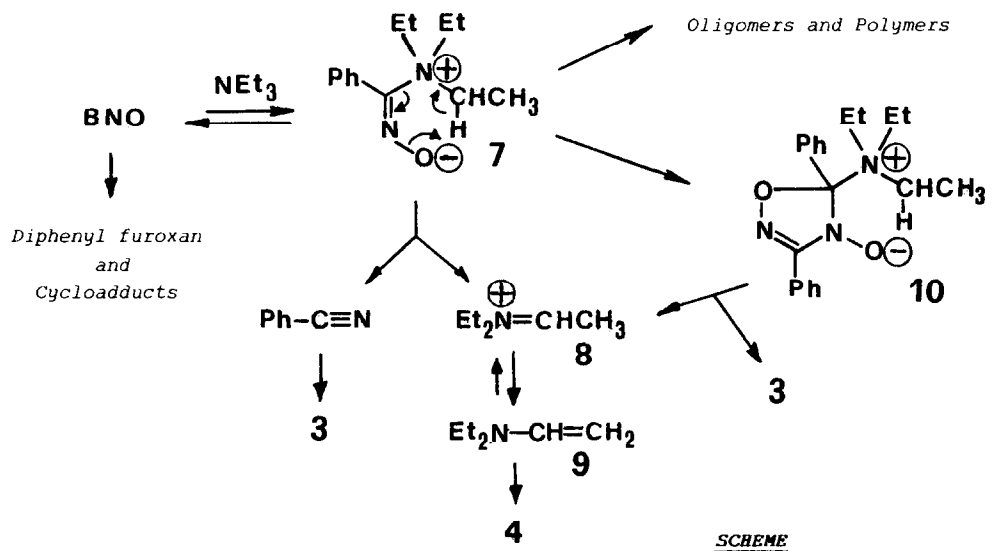
TLC examination of the different runs neatly shows the increase of the oxadiazole/furoxan ratio with increasing triethylamine and the appearance of several additional products. In the runs in ether, benzene and methylene chloride, excess triethylamine induces the formation of a definite spot at $R_f \sim 0.4$ (ethyl acetate:cyclohexane 3:7), while in ethanol the spot is faded. The product was isolated by column chromatography from a reaction of benzhydroximic acid chloride and 10 equiv triethylamine in methylene chloride. A colourless oil was obtained and identified as 3-phenyl-5-diethylamino-2-isoxazoline 4 (12% yield). Structure 4 follows from the NMR spectrum (δ, $CDCl_3$: 1.10 t (6H, $\underline{CH}_3$), 2.55 q (4H, $\underline{CH}_2CH_3$), 3.02 m (2H, geminal H_4), 5.6 dd (1H, H_5, J=6 and 9 Hz), 7.2-7.7 m (5H, aromatics)), and from its transformation into 3-phenyl-isoxazole 5 under acidic conditions (HOAc/50%H_2SO_4 1:1, 0.5 h reflux). Isoxazoline 4 is rather unstable. On standing in moist solvent or by slow column chromatography, 4 exchanges the diethylamino group with OH, yielding the known 3-phenyl-5-hydroxy-2-isoxazoline 6[8].



4 5 6

The fragmentation

The set of the results discussed so far points out that triethylamine and polar solvents induce the formation of 3,5-diphenyl-1,2,4-oxadiazole through a reaction path which competes with the dimerization and cycloaddition reactions of BNO. Minor amounts of benzonitrile were also noted. Moreover dehydrogenation of triethylamine occurs, as inferred from the isolation of isoxazoline 4. A reasonable mechanism involves zwitterion 7, as shown in the Scheme.



SCHEME

Nucleophilic addition of triethylamine to the nitrile oxide carbon affords the labile adduct 7. The adduct can revert to the reactants[3] or undergo further addition of BNO at the negative oxygen, yielding oligomers and polymers[5]. Alternatively zwitterion 7 (or its oligomeric O-derivatives), could fragment into benzonitrile and the immonium salt 8. This latter is deprotonated in the basic medium, yielding enamine 9 or is trapped in ethanol. Cycloadditions of BNO to benzonitrile and enamine 9 afford then oxadiazole 3 and isoxazoline 4, resp. The Scheme satisfactorily accounts for all the products observed. However only a part of oxadiazole can derive from this route, because of the low dipolarophilic activity of benzonitrile[6]. Control experiments show that only a 22% yield of oxadiazole is produced by cycloaddition of BNO to 1 equiv benzonitrile. A conceivable alternative is the cycloaddition of BNO across the C=N bond of zwitterion 7 or its O-derivatives. The C=N bond of these species combines a nucleophilic nitrogen with a highly activated electrophilic carbon. The adduct, 10, can fragment directly into oxadiazole and immonium salts.

Aside from clarifying the mechanism of oxadiazole formation, the results lend themselves to further application to other 1,3-dipoles. The related diphenyl nitrile imine is usually generated in situ from benzhydrazonoyl chloride and affords 1,3,5-triphenyl-1,2,4-triazole as a side product[9]. The hitherto unexplained formation of this triazole could occur through a fragmentation similar to that shown in the Scheme.

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