DIAZONIUM COUPLING REACTION OF SOME DIAZINE N-OXIDES

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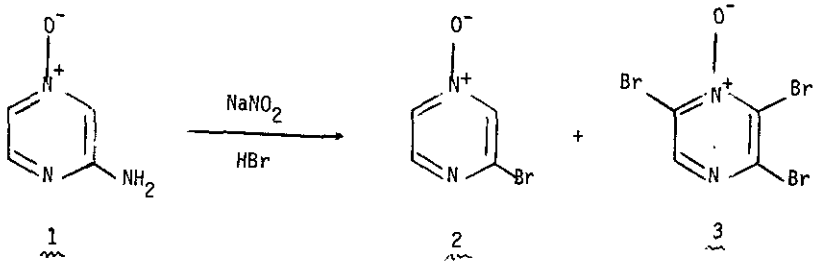
Abstract -Attempted deoxygenation of 2-aminopyrazine 1-oxide with HF under the diazotization conditions yielded a coupling reaction product, 2,2'-bispyrazyltriazine 1,1'-dioxide. Similarly, diazotization of 2-aminopyrimidine 1-oxide in the presence of hydrofluoric acid gave a nucleophilic hydroxylative-deoxygenation product, 5-hydroxy-2-pyrimidinediozotic acid.

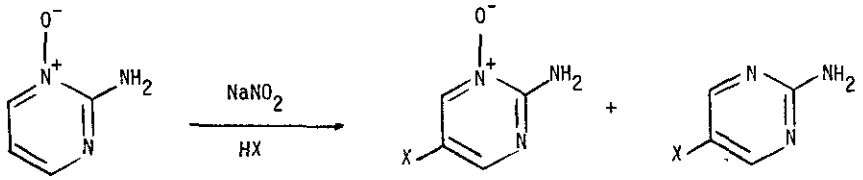
Recently, we have described the diazotization of several aminodiazine N-oxides.[1] In addition to the expected halo derivatives, some electrophilic substitution products were also isolated. For instance, 3-aminopyrazine 1-oxide (1) gave 2,3,6-tribromopyrazine 1-oxide (3) as well as the expected 3-bromopyrazine 1-oxide (2). The formation of 3 was accounted for by the bromination of 1, reported elsewhere,[2] followed by diazotization of the resulting 2,6-dibromo-3-aminopyrazine 1-oxide (4).



1 2 3

Similar pattern was observed for 2-aza analog of 1 where 3-amino-1,2,4-triazine 1-oxide yielded 3,6-dibromo-1,2,4-triazine 1-oxide via halogenative diazotization.[3] The same applied to 2-aminopyrimidine 1-oxide (5) where electrophilic halogenation preceded diazotization to produce 5-halo-2-aminopyrimidine 1-oxides (6a, 6b) and some 5-halo-2-aminopyrimidines (7a, 7b). Evidence was presented to show that

deoxygenation products 7a and 7b arose by halogenation via addition-elimination sequence and paralleled the behavior of 3-amino-1,2,4-triazine 2-oxides.[3,4]



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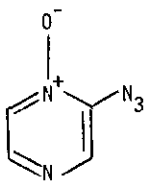
6a X=Cl
6b X=Br

7a X=Cl
7b X=Br

The goals of this publication were to prepare fluoro π-deficient N-oxides, to study the propensity towards nucleophilic substitution of fluoride ion vs that of solvent, starting material, etc., and to explore the possible deoxygenation and fluorination of diazine N-oxides by HF.

In order to determine whether hydrogen fluoride would promote any of the side reactions discussed above, we subjected 2-aminopyrazine 1-oxide (8) to the cold solution of 40% hydrofluoric acid containing sodium nitrite for 48 h to obtain the product, 9, which immediately started to turn gray and almost entirely decomposed within two days. Its ^1H nmr spectrum (see Table I) is very similar but not identical to that of known 2-azidopyrazine 1-oxide (10)[5], also prepared by us by reacting the corresponding halo derivatives (11 and 12) with sodium azide in aqueous acetone. To complicate the matter, the mass spectrum of 9 contained only



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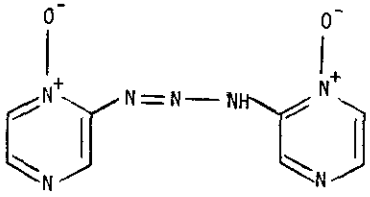

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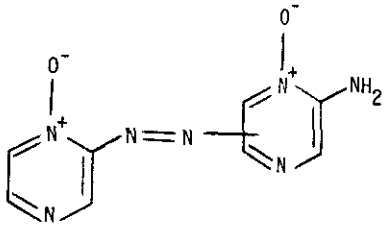
three prominent fragment ion losses above 10% intensity (m/e 137, 109, 93) also characteristic of 10. However, appearance of the molecular ion at m/e 232, together with the elemental analysis, confirmed the assigned structure of 9 to be that of a coupled compound, 2,2'-bispyrazyltriazene 1,1'-dioxide. The isolation of intermolecular coupling reaction product (9) is consistent with the fact that the fluoride ion is a poorer nucleophile than a heterocyclic amine (8).

When the same reaction was quenched after 20 min, a miniscule amount of a bright yellow compound (13) was obtained. The elemental analysis indicated a molecular formula of $C_8H_7N_7O_2$ and mass spectrum of 13 showed a parent peak of 233 with losses of m/e 111 and m/e 28 fragments. From this information and the ir band at 1620 cm^{-1} it was concluded that intermolecular coupling had taken place where compound 8 had undergone the electrophilic ring substitution by its diazonium salt to produce the azo derivative (13). Because of the small quantity of this material, no attempt was made to identify the substitution site, but it is reasonable to assume from results of electrophilic halogenation,[1,2] that the compound 13 is the C_5 isomer.



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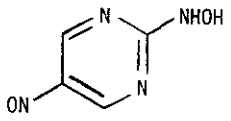
In view of these results, the same reaction was extended to pyrimidine N-oxides. When the diazotization was carried out on 2-aminopyrimidine 1-oxide (14) with nitrous acid in the presence of HF, compound 15 with a molecular formula $C_4H_4N_4O_2$ was isolated. Its mass spectrum showed a strong loss of both the N_2 and of one OH fragment. The ^1H nmr spectrum of 15 had a singlet at δ8.70 ppm (see Table II) indicating that a symmetrical 2,5-disubstituted pyrimidine was formed in this reaction. From the several possible structures (16, 17, 18), compound 17 can be



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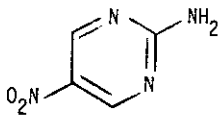

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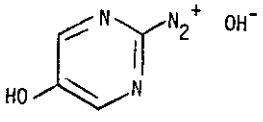

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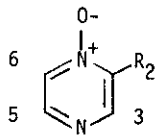
eliminated by comparison with an authentic sample (^1H nmr, δ9.15 ppm). Substance 16 is expected to be colored, yet 15 is not and both 16 and 17 would have ir bands characteristic of their functionalities (nitroso and nitro groups). Furthermore,

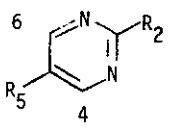
TABLE I. ^{1}H NMR Data of Some 2-Substituted Pyrazine 1-Oxides



Cmpd No.	Molecular Formula	Substituent (R)	Chemical Shifts[a,b] R_2	R_3	R_5	R_6	Coupling Constants (Hz) $J_{3,5}$	$J_{3,6}$	$J_{5,6}$
8	$C_4H_5N_3O$	NH_2	7.35[c]	8.55	8.51	8.12	-	-	4.0
			6.80[d]	8.25	7.99	7.73	-	-	4.0
9	$C_8H_7N_7O_2$	$C_4H_4N_5O$	-	8.24	8.22	8.07	-	0.8	4.5
10	$C_4H_3N_5O$	N_3	-	8.25	8.16	8.08	0.5	-	4.5

[a] All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated. [b] δ(ppm) downfield from TMS. [c] D_6-DMSO. [d] $CDCl_3$ and D_6-DMSO.

TABLE II. ^{1}H NMR Data for Selected Pyrimidines



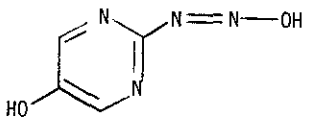
Cmpd. No.	Molecular Formula	mp, °C[a]	Substituents R_2	R_5	Chemical Shifts[b,c] R_2	R_4	R_5	R_6	Coupling Constant (Hz) $J_{4,5}$	$J_{4,6}$	$J_{5,6}$
14[d]	$C_4H_5N_3O$	186-188	NH_2	-	8.07	8.79	7.12	8.27	6.0	2.0	5.0
15	$C_4H_4N_4O_2$	110(dec.)	N_2OH	OH	-	8.60	-	8.60	-	-	-
17[e]	$C_4H_4N_4O_2$	235-237	NH_2	NO_2	8.44	9.28	-	9.28	-	-	-

[a] Melting points were uncorrected. [b] All spectra were recorded as dilute solutions in D_6-DMSO. [c] δ(ppm) downfield from TMS. [d] N_1-oxide. [e] This compound was commercially available.

the mass spectral fragmentation pattern of 15 is not consistent with either structure. Diazonium hydroxide analog fits best the experimental results. Due to the lack of $-N_2^+$ absorption (~2250 cm^{-1}) in the infrared spectrum of 15 and inability of 15 to couple with β-naphthol in alkaline solution, we have further

modified the structure of 15 and assigned it to be that of an isomeric 5-hydroxy-2-pyrimidinediazotic acid.

The introduction of the hydroxyl group at C_5, concurrent with deoxygenation, is consistent with the formation of 7a and 7b and follows the same mechanistic path[1] (i.e. formation of 2-amino-5-hydroxypyrimidine followed by diazotization of the amino function). The isolation of diazotic acid (15) also reflects the poor



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nucleophilicity of the fluoride ion as compared to chloride and bromide ions. Since 2-aminopyrimidine 1-oxide (14) couples with the diazonium salt of p-toluidine at the amino group,[6] it appears that during the diazotization of 14, the deoxygenation and formation of the 5-hydroxy derivative precedes the diazotization step.

EXPERIMENTAL

2-Azidopyrazine 1-Oxide (10). A solution of 130.5 mg (1.0 mmol) of 2-chloropyrazine 1-oxide (11) in 20 ml of 80% aqueous acetone was left standing at room temperature for 48 h in the presence of 143 mg (2.2 mmol) of sodium azide, after which time it was concentrated under reduced pressure and extracted with chloroform (3 x 10 ml). The combined organic extracts were dried, filtered and evaporated to dryness to give 98.6 mg (72%) of a grayish-tan solid consisting of almost pure 10, mp 84-85.5°C (lit. 85-87°C).[5]

Compound 10 was also made from fluoro derivative (12)[7] in 80% yield.

Reaction of 2-Aminopyrazine 1-Oxide (8) with $NaNO_2$/HF. In a typical experiment, 180 mg (1.6 mmol) of 8 was dissolved in 1.5 ml of 40% HF. This mixture was cooled to 0°C and to it was added dropwise, over a period of 15 min, a solution of 210 mg (3.0 mmol) of $NaNO_2$ in 0.8 ml of water. After the addition was completed, the reaction mixture was allowed to come to room temperature, kept there for another 15 min, and extracted with 5 x 8-ml portions of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2CO_3, filtered, and CH_2Cl_2 was evaporated *in vacuo* to furnish 55 mg (17%) of 2,2'-bispyrazyltriazene 1,1'-dioxide (9); mp 51°C (dec.).

This compound was light sensitive and decomposed readily at room temperature within a few hours.

Preparation of 2-Amino-2',5-bisazopyrazine 1,1'-Dioxide (13). This procedure was identical to the one described above except that solution was made basic with saturated sodium carbonate (pH ~ 9) before it was brought to room temperature. Upon workup, bright yellow powder was isolated in 5% yield, mp > 300°C. Anal. Calcd. for $C_8H_7N_7O_2$: C, 41.20; H, 3.03; N, 42.05. Found: C, 41.23; H, 2.99; N, 41.87. No attempt was made to differentiate the 2',5-bispyrazyl isomer from that of 2',6-isomer. We assigned the structure of 13 to be the former on the basis of the previous substitution studies.[1,2]

Reaction of 2-Aminopyrimidine 1-Oxide (14) with $NaNO_2$/HF. This procedure was carried out in the same manner as described for the preparation of compound 9 except that 14 was used as the starting material instead of substance 8. The extraction with ethyl acetate furnished compound 15 in 12% yield. Anal. Calcd. for $C_4H_4N_4O_2$: C, 34.28; H, 2.88; N, 39.99. Found: C, 34.21; H, 2.95; N, 40.30 (also see Table II).

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