FLUOROHETEROCYCLES II. SYNTHESIS OF 3-FLUORO-1,2,4-TRIAZINE 2-OXIDES[1]

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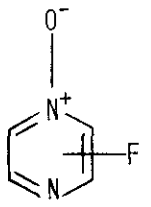
Abstract - Selected 3-fluoro-1,2,4-triazine 2-oxides were prepared by nitrosation of respective amino compounds and thermolysis of the corresponding diazonium tetrafluoroborate salts. In one instance, the intermediate diazonium salt was isolated; the first stable heterocyclic diazonium salt ever reported.

Based on a well established pharmacological axiom, fluorinated heterocycles have a great potential for biological activity.[2] There is an abundance of literature reports on polyfluorinated heterocyclic systems but very few such reports exist on monofluoro compounds and particularly their N-oxides.[3] One of the possible explanations could be that the most common method employed for their synthesis, the high temperature halogen exchange reaction, results in decomposition and deoxygenation of the parent heterocycle.

We have recently prepared some fluoropyrazine N-oxides 1a and 1b by three different methods.[1] Even more intriguing was the finding that 1,3-diazines and

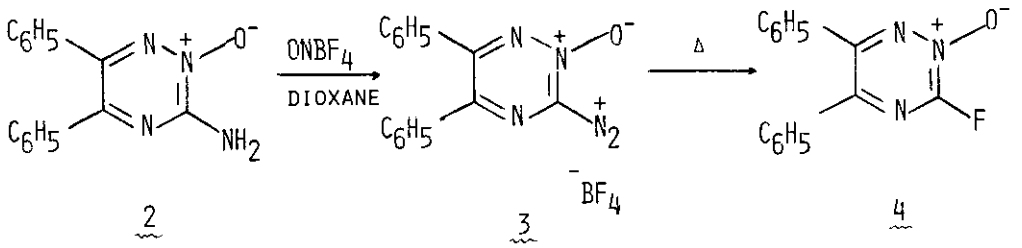


1a 2-FLUORO

1b 3-FLUORO

polyazines may undergo of a variety of addition-elimination and substitution reactions in the presence of HF and other hydrohalic acids and thus offer unusual and new methods for the preparation of otherwise inaccessible compounds. Due to the low nucleophilicity of the fluoride ion, one can selectively introduce a number of functional groups. In such a manner, one can achieve halogenation, nitrosation, alkoxylation and hydroxylation of pyrimidine and 1,2,4-triazine ring.[4-8]

When 3-amino-5,6-diphenyl-1,2,4-triazine 2-oxide (2) was treated with nitrosonium tetrafluoroborate in dry dioxane, it immediately formed the powdery yellow solid 3 which, when heated with or without the solvent, yielded the desired 3-fluoro-5,6-diphenyl-1,2,4-triazine 2-oxide (4).



2 3 4

Diazonium salt (3) was unusually stable and once isolated could be kept at room temperature under an inert atmosphere (N_2) for several weeks. To our knowledge, this is the first isolable heterocyclic diazonium salt ever reported. The structural assignment was based on the mass spectrum (molecular ion 363 m/e with prominent boron isotopes) and its infrared spectrum (suspension of 3 in chloroform has a strong absorption at 2260 cm^{-1} characteristic of $-\overset{+}{N}\equiv N$ stretching vibration - Figure 1). The parent peak of 363 mass units for 3 is unusual in a sense that structure 3 as depicted above consists of two particles. We attributed the combined parent peak to the intermediates such as $[\ \rangle N\text{-}O\text{-}BF_3]^{\bullet}$, $[\ \rangle\overset{+}{N}\text{-}BF_3]^{\bullet}$ or any other similar intermediate which could be produced as a result of the radical coupling reaction in the vacuum chamber.

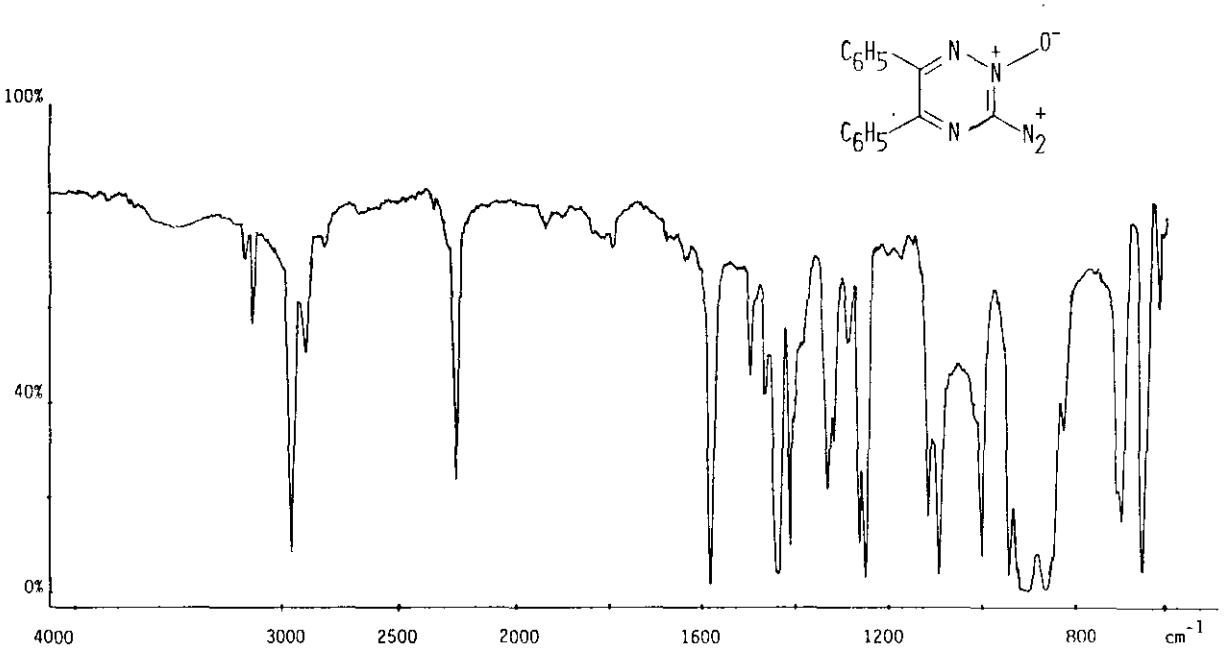
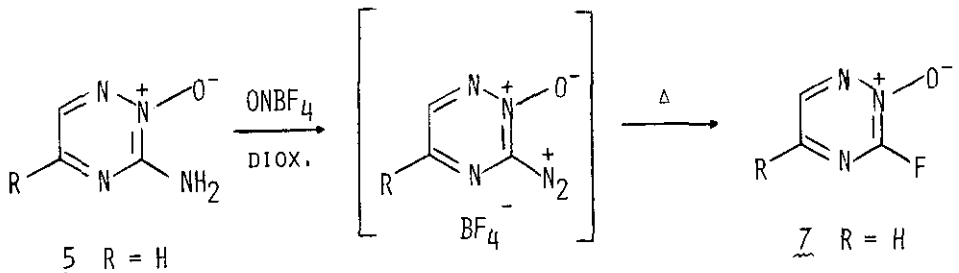


Fig. 1 The ir spectrum of compound 3 as a suspension in chloroform.

Interestingly enough, the diazonium tetrafluoroborate salts of 3-amino-1,2,4-triazine 2-oxide (5) and 3-amino-5-phenyl-1,2,4-triazine 2-oxide (6) could not be isolated as stable solid materials. Instead, they produced reddish-brown viscous oils which were pyrolyzed to the corresponding 3-fluoro- (7) and 3-fluoro-5-phenyl-1,2,4-triazine 2-oxide (8). The higher stability of 3 may be due to the presence of both phenyl groups which through resonance are better able to distribute the additional charge (9a-e).

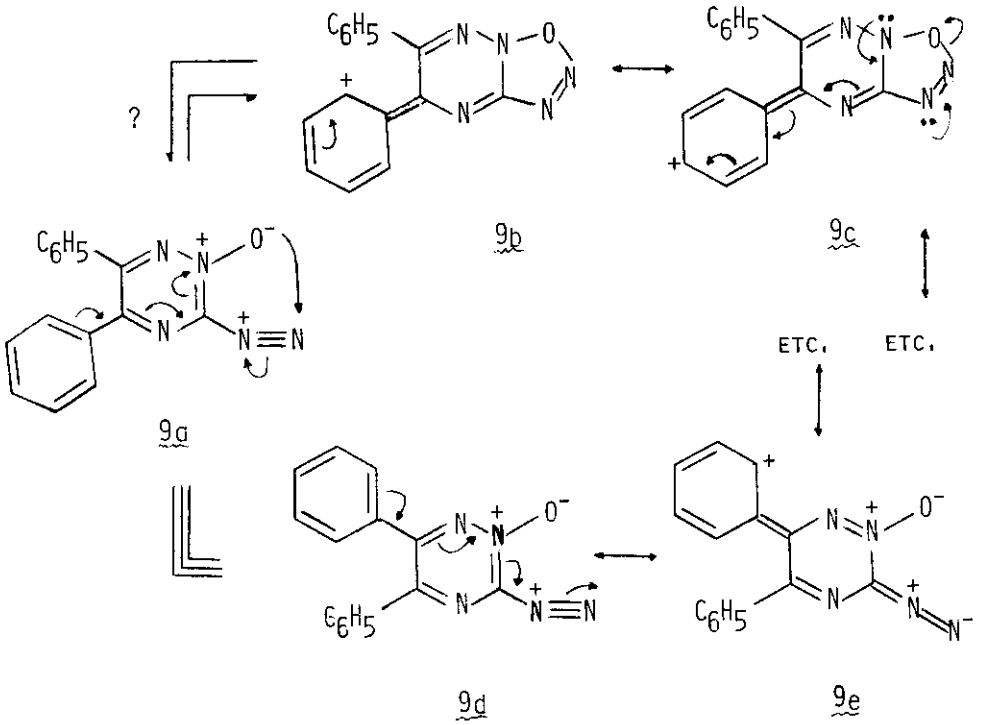


5 R = H

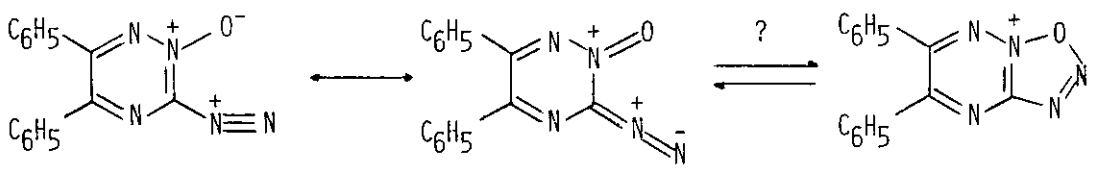
6 R = C_6H_5

7 R = H

8 R = C_6H_5

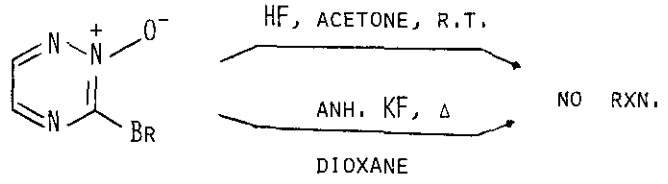


The intermediacy of oxatriazolotriazine (9b) is highly questionable in view of the infrared data (-N=N- stretching vibrations have absorptions in the infrared region of 1576 cm^{-1}) and the instability induced by bonding four heteroatoms to each other. This arrangement would be particularly unfavorable if in addition to that the bridgehead nitrogen (N_2) would carry a charge (as by N-oxide participation in 10c). Therefore, only the phenyl group in the six position adds significantly to the overall stability of the diazonium ion of 3.



Attempts to prepare 4, 7 and 8 by Balz-Schiemann method, used successfully with aminopyrazine N-oxides [1], failed with 3-amino-1,2,4-triazine N-oxides. In most instances, starting material was recovered and when the temperature was raised above 0°C, extensive decomposition occurred. Direct N-oxidation of 3-fluoro-1,2,4,-triazines to their respective N-oxides was not possible because of their great instability and the fact that 1,2,4-triazines are preferentially oxidized at C_5 rather than the ring nitrogen atom(s).[9]

3-Bromo-1,2,4-triazine 2-oxide (11) remained unchanged when treated with one equivalence of HF in acetone at room temperature. The halogen exchange with anhydrous potassium fluoride in dry dioxane at reflux temperature also failed and high temperature reactions under a variety of different reaction conditions[10-14] resulted in decomposition of 1,2,4-triazine ring.



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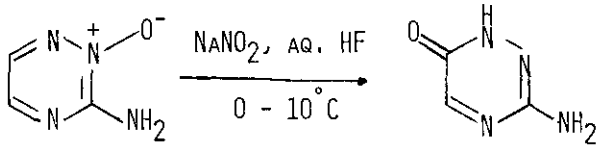
However, diazotization of 3-amino-1,2,4-triazine 2-oxide (5) with sodium nitrite in the presence of HF gave 3-amino-5,6-dihydro-1,2,4-triazine-6-one (12). β-Hydroxylation with deoxygenation of 1,2,4-triazine ring was expected in view of



5 12

our previous results.[4,7] What is striking is that the amino group remained unchanged. This supports our earlier claims that deoxygenation precedes the diazotization of the exocyclic amino groups.[4,15] The rate determining step seems to be the protonation of the N-oxide oxygen atom. Once that is achieved, the addition of the anion (or in this case, the solvent molecule - water) the elimination of the N-oxide oxygen is rapid. The degree of competition between

this reaction and the diazotization of the amino group is determined by nucleophilicity of the two atoms. Since diazotization requires the low pH medium (1-4), we repeated the above reaction with excess of hydrofluoric acid but were not able to isolate any other products. Thus, the subtle difference between aminopyrimidine N-oxides and amino-1,2,4-triazine N-oxides is that the nitrogen of the amino group in the former compounds is more nucleophilic and, therefore, is diazotized more readily. Scheme I lists the products obtained from the reaction of various aminoazine N-oxides with HF and nitrous acid under identical reaction conditions.

Scheme I

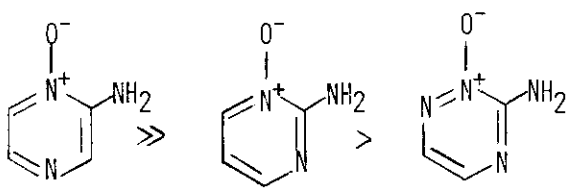
Reaction of same aminoazine N-oxides with $HF/NaNO_2$

	2-aminopyrazine* 1-oxide	2-aminopyrimidine 1-oxide	3-amino-1,2,4-triazine 2-oxide
Product:	2,2'-bispyrazyl triazene 1,1'-dioxide	5-hydroxy-2-pyrimidine diazotic acid	6-hydroxy-3-amino 1,2,4-triazine (12)

*under basic conditions (pH=9) the azo derivative, 2-amino-5,2'-azopyrazine 1,1'-dioxide is produced.[1]

Another striking feature of this comparison is the correlation which exists between the π_Δ values recently developed by our group [16-18] and the reactivity of simple heterocycles. The nucleophilicity of the amine nitrogen atom is to a large extent determined by the "degree" of the electronic pull exerted by the π-deficient ring. In a sense, the six-membered ring acts as a powerful -I substituent on the amino group. Therefore, the more ring nitrogens that are present, the less likely is the amino group going to become a nucleophile (as with aminopyrazine N-oxides) or be nitrosated (1,2,4-triazine vs pyrimidine N-oxides). Scheme II summarizes these results and nicely demonstrates the validity of this approach. This may

Scheme II

Nucleophilicity:  $\gg$ $>$

π_Δ values[a]:	1.00	0.77	0.64

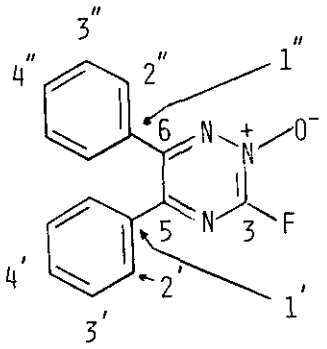
a. taken from reference 18.

also explain in part the propensity of 1,3-diazine and polyazine N-oxides to undergo β-addition/N-oxide elimination reactions.

Attempted diazotization of 5 under unhydrous conditions failed. Thus, when 5 was dissolved in absolute ethanol and treated with isoamylnitrite in the presence of HF, only starting material was recovered.

NMR DATA

We have already described and analyzed proton NMR spectra of some fluoropyrazine N-oxides.[1] In this instance, they were not as valuable for structural assignments due to the lack of ring protons and/or extensive overlapping of signals (Fig. 2a). More direct approach was to obtain the ^{13}C spectra since ^{13}C - ^{19}F coupling constants much more clearly indicate the presence of fluorine in the molecule and pattern of substitution. For instance, proton decoupled ^{13}C spectrum of 4 is reduced to the first order spectrum (Fig. 2b) and can, thus, be easily interpreted. *Any significant* ^{13}C - ^{19}F *coupling only takes place over four* bonds.[19] Therefore, the most likely carbon resonances to appear as a doublet would be those of C_3, C_5, C_6 and $C_{1''}$. We find this indeed to be the case



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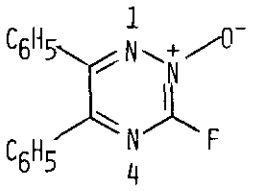
and when averaged, the sets of the resonances at 161.5, 139.7 ppm; 137.0, 135.6 ppm; 130.8, 128.0 ppm; 129.7, 125.5 ppm gave the chemical shifts of C_3 (145.6 ppm), C_6 (136.3 ppm), $C_{1''}$ (129.4 ppm), and C_5 (127.6 ppm), respectively. The assignments were made based on several criteria, the most important of which was the size of ^{13}C - ^{19}F coupling constants. *There is no question that* C_3 would show the largest such coupling, 218 Hz (as compared to J_{C_1F} of 238.3 Hz and J_{C_2F} of 245.3 Hz for 2-fluoropyridine[20] and fluorobenzene[21], respectively). The three



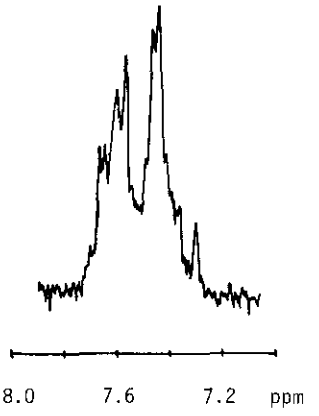


FIG. 2a

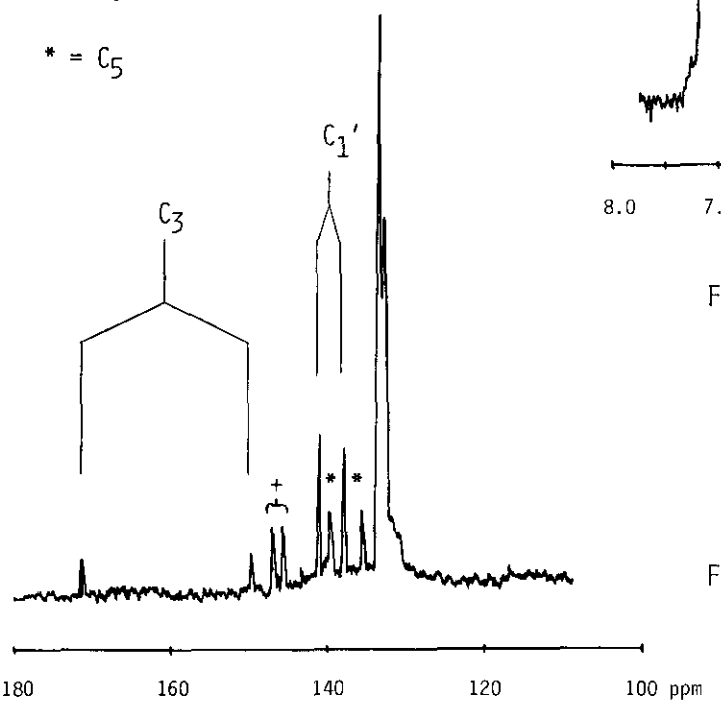


FIG. 2b

Fig. 2a Proton nmr spectrum of compound 4 (aromatic region).

Fig. 2b Expanded aromatic region of proton-decoupled ^{13}C spectrum of 4.

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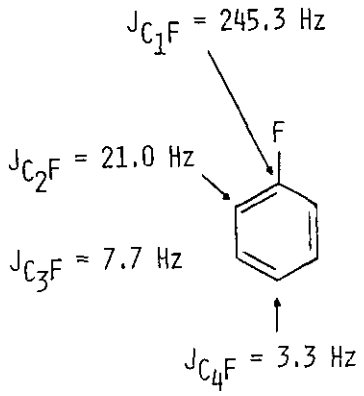
bond ^{13}C - ^{19}F coupling (J_{C_5F} = 42 Hz) also compares favourably with that reported for pyridines (J_{C_6F} = 15.5 Hz). The two sets of overlapping doublets at the higher field were assigned to $C_{1'}$ and C_6. The question of the validity of their assignment is easily answered if one compares the ^{13}C - ^{19}F coupling constants of fluorobenzene (13) with those of 2-fluoropyridine (14).



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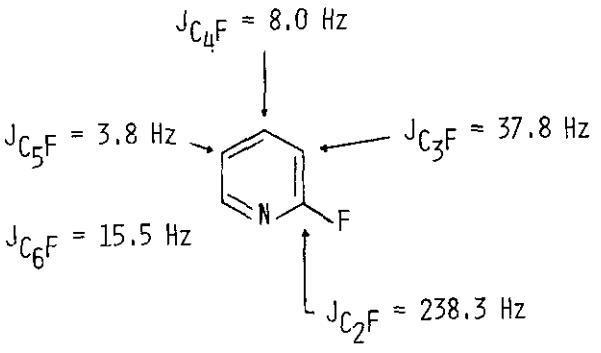

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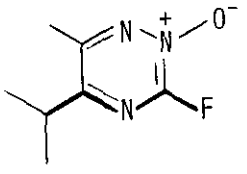
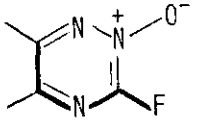
It is obvious that the magnitude of ^{13}C - ^{19}F coupling decreases with the distance between the two atoms. Furthermore, the ^{13}C - ^{19}F coupling is larger across the nitrogen atom than across the equivalent carbon atom ($J_{C_6F} > J_{C_4F}$). This change in bond order caused by additional ring nitrogens explains why the analogous coupling constants in 1,2,4-triazines are larger than the corresponding carbon - fluorine coupling in 13 and 14. The choice made for the assignments of C_1, and C_6 was based on the signal intensity (ring carbon atoms adjacent to heteroatoms have considerably longer relaxation time)[21] and the fact that C_1, and fluorine exist in the familiar "W" configuration and C_6 and F do not. Thus, $J_{C_1,F}$ should be larger than J_{C_6F}.



$J_{C_1'F}$ = 28 Hz

"W" CONFIGURATION



J_{C_6F} = 14 Hz

NOT A "W" CONFIGURATION

Carbon resonances of the two phenyl groups appear as two considerably larger signals at 122.5 and 123.2 ppm. They are almost identical to the two phenyl resonances of 2, which appear at 126 and 127 ppm. Other chemical shifts for 2

were assigned as: C_3, C_5, C_6, $C_{1'}$ and $C_{1''}$ at 146.1, 138.0 139.5, 132.3 and 133.5 ppm, respectively, based on model compounds such as 5 (C_3 = 151 ppm, C_5 = 132 ppm, C_6 = 134 ppm)[22]. The ^{13}C chemical shifts of compound 5 reported in literature are undoubtedly correct since the authors have established that the 5-methyl compound only changes the chemical shift of the substituted carbon atom and that the other two resonances remain the same as in 5.[22]

The complete analysis of ^1H and ^{13}C spectra of other fluoro-1,2,4-triazines and their N-oxides will be the subject of our forthcoming communication but the ^{13}C nmr data of compounds 7 and 8 are included herein for reference purposes. Compound 7 in d_6-DMSO/d_6-acetone: C_3, 149.8; C_5, 122.1; C_6, 131.5 ppm. Compound 8 in d_6-DMSO: C_3, 149.5; C_5, 131.0; C_6 130.6; $C_{1'}$, 128.1; $C_{2'}$, $C_{3'}$ and $C_{4'}$ at 125.4 and 122.8 ppm.

EXPERIMENTAL

Starting Materials. Compounds 2, 5 and 6 are known and were prepared by procedures cited in literature.[22,23] ^{13}C nmr of compound 6 in d_6-DMSO (39.5 ppm): C_3, 150.3; C_5, 141.2; C_6, 133.6; $C_{1'}$, 130.2; $C_{2'}$, $C_{3'}$ and $C_{4'}$ at 128.9 and 126.3 ppm. ^{13}C chemical shifts for compound 2 in the text are referenced to the external TMS standard; referenced to the solvent (d_6-DMSO at 39.5 ppm); C_3, 149.4; C_5, 140.9; C_6, 142.4; $C_{1'}$, 134.8; $C_{1''}$, 135.9; phenyl carbon atoms at 128.2 and 129.2 ppm.

Reaction of 3-Amino-5,6-diphenyl-1,2,4-triazine 2-Oxide (2) with Nitrosonium Tetrafluoroborate. To 150 ml of dry dioxane (distilled several times from sodium) was added 1.0 g (3.8 mmol) of 3-amino-5,6-diphenyl-1,2,4-triazine 2-oxide (2). The mixture was stirred until all of the solid dissolved and 1.4 g (8.56 mmol) of $ONBF_4$ in 30 ml of dioxane was added over a period of 5 min. Within minutes, yellow powdery solid precipitates from the red solution. It was immediately collected (it redissolves in 30 min.), dried with nitrogen gas and stored. The diazonium salt (3) was very stable under inert atmosphere and could be kept at room temperature for several weeks. During that time, a small evolution of nitrogen oxides was observed. However, when 3 was exposed to air, it reacted vigorously (it explodes and should be handled with care); it detonates on impact or when heated above 50°C, thus preventing elemental analysis. It was decomposed in 20 ml of water and 20 ml of acetic acid. Extraction of the aqueous layer with CH_2Cl_2

(4 x 30 ml), drying the combined organic layers over magnesium sulfate, filtration and evaporation of the solvent in vacuo yielded the unstable *iminobenzaldehyde* (^{1}H nmr) which soon polymerized.

The structure of 3 was assigned on the basis of its mass spectrum (M^+ at 363 m/e with boron isotopes; loss of 28 m/e and 16 m/e) and its infrared spectrum (ν at 2260 cm^{-1}). Compound 3 reacted with sodium chloride (white gas thought to be HF or BF_3 was given off). However, the infrared spectrum of the fine suspension of 3 in chloroform verified the presence of diazonium salt. (Figure 1 shows a traced spectrum).

Decomposition of 3 to 3-Fluoro-5,6-diphenyl-1,2,4-Triazine 2-Oxide(4). Solid 3 or the viscous brown oil, obtained by evaporating the dioxane solution, were *pyrolyzed under vacuum* (70 torr) and the transparent, pale yellow crystals which sublimed were collected (dec. 114°C). The mass spectrum (mol. wt. 267, loss of 16 m/e and 19 m/e) and ^{1}H, ^{13}C nmr unmistakably identified this compound as 3-fluoro-5,6-diphenyl-1,2,4-triazine 2-oxide(4).

Similarly, 3 was thermally decomposed in dimethyl sulfoxide to yield 4 as long yellow needles. In such a manner, the ^{13}C nmr sample of 4 was prepared; i.e. 700 mg (2 mmol) of 3 were heated in 1.5 ml of d_6-DMSO until the effervescence ceased. The cooled sample contains approximately 1.2 - 1.5 M solution of 4. (Fig. 2a and 2b).

Reaction of 3-amino-1,2,4-triazine 2-Oxide(5) with Nitrosonium Tetrafluoroborate. This procedure was identical to the one described above with the exception that the diazonium tetrafluoroborate salt was not isolated. Instead, 448 mg (4.0 mmol) of 3-amino-1,2,4-triazine 2-oxide (5) were dissolved in 120 ml of dry dioxane and *treated with 1.4 g of* $ONBF_4$. The resulting red solution was evaporated after 2 h and the remaining thick, orange oil pyrolyzed to yield 193.2 mg (42%) of 3-fluoro-1,2,4-triazine 2-oxide (7) (mp 28°C, dec.; ^{1}H nmr, two multiplets at δ 8.32 and δ 8.68 ppm in $CDCl_3$).

Similarly, compound 8 was prepared from 6 in 37% yield.

Attempted Conversion of 3-Amino-1,2,4-triazine 2-oxide(5) to 3-Fluoro-1,2,4-triazine 2-oxide (7) by Balz-Schiemann reaction. 1.79 g (16 mmol) of 5 was treated with 1.2 g (17 mmol) of sodium nitrite in 1.5 ml. of water as described in literature.[1] Upon workup, starting material was recovered. Diazotization of 5

above 0°C produced an intractable white solid which upon further analysis proved to be a polymer.

Attempted Deoxygenation of 3-Bromo-1,2,4-triazine 2-Oxide (11) with HF. Compound 11 (50 mg, 0.29 mmol) was dissolved in "tech grade" acetone. To this solution was added 5.72 mg of 50% HF (0.29 mmol, 8 µl) and whole stirred at room temperature. After 24 h the pale yellow solution was evaporated to yield unchanged 3-bromo-1,2,4-triazine 2-oxide (11). Subsequently, even when 11 was treated with excess of hydrofluoric acid, it was recovered almost quantitatively and no deoxygenated products were observed.

Attempted Halogen Exchange of 11 with Anhydrous KF. 3-Bromo-1,2,4-triazine 2-oxide (11) (175 mg, 1.0 mmol) was refluxed in dry dioxane with anhydrous potassium fluoride (216 mg, 2.3 mmol) for 45 min. The resulting solution was cooled and evaporated to dryness to yield the starting material. Solvation of the cation with small amounts of crown ether did not change the outcome of the reaction.

Reaction of 5 with $NaNO_2$/HF. In a typical experiment, 112 mg (1.0 mmol) of 5 was dissolved in 1.5 ml of 40% HF. This reaction mixture was cooled to 0°C and to it added dropwise a solution of 100 mg (1.5 mmol) of sodium nitrite in 1.0 ml of water. After the addition was completed (15 min), the reaction mixture was slowly brought to room temperature, kept there for an additional 20 min, and extracted with 50:50 acetonitrile/CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and solvent evaporated to give 34.7 mg (31%) of 3-amino-5,6-dihydro-1,2,4-triazine-6-one (12) as a white solid (mp 182-184°C, lit. 184°C [24]; H_5, δ 8.68 ppm in d_6-DMSO).

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