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Thermal- and Photo-induced Transformations of *N*-Aryl-*N*-nitrosohydroxylamine Ammonium Salts to Azoxy Compounds

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Abstract: Heating of an ethanolic solution containing *N*-aryl-*N*-nitrosohydroxylamine ammonium salts at 78 °C produced the desired azoxy compounds in 80–93% yields. Furthermore, irradiation with UV light (λ ≥300 nm) of ethanolic solutions of those ammonium salts at room temperature also provided the desired azoxy compounds in 51–72% yields. © 1997 Elsevier Science Ltd.

Established methods for the generation of azoxy compounds include oxidation of amines[2] and azo compounds,[3,4] reduction of nitro[5] and nitroso compounds,[6] and coupling of nitroso compounds with hydroxylamines.[7,8] Those methods require oxidizing[2–4] or reducing[5,6] agents, or use of unstable hydroxylamines[7,8] as the starting materials. Herein we report a new process, which can lead *N*-aryl-*N*-nitrosohydroxylamine ammonium salts to acyclic and cyclic azoxy compounds. This transformation is induced by heat or UV light.

We added *N*-phenyl-*N*-nitrosohydroxylamine ammonium salt[9,10] (**1a**) to various solvents (0.10 M), including acetone, acetonitrile, benzene, *N*,*N*-dimethylformamide, ethanol, ethyl acetate, *n*-hexane, tetrahydrofuran, and water. The solubility of **1a** in the aforementioned solvents is listed in Table 1. The mixture was then heated at reflux for 2.0 h to produce the corresponding azoxy compound **2a** in 15–85% yields after purification by chromatography; the highest yield was obtained by use of ethanol as the solvent. To realize its generality, we performed the same type of reaction by using **1b–m** as the substrates in ethanol (see Schemes 1 and 2). The desired azoxy compounds **2b–m** were isolated in 80–93% yields (Table 2). Furthermore, we irradiated the ethanolic solutions of **1a–m** (0.015 mM) with a 450-W medium-pressure mercury UV lamp through a Pyrex filter (λ ≥300 nm) at room temperature for 2.0 h. The corresponding pure azoxy compounds **2a–m** were obtained in 51–72% yields (see Table 2).

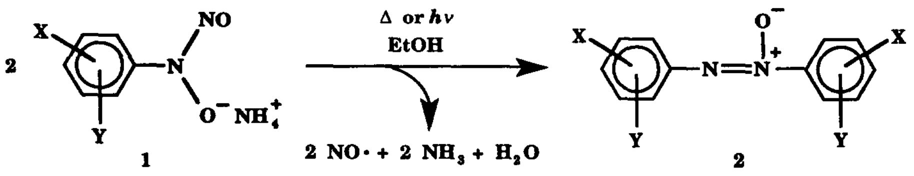
These new methods for the preparation of azoxy compounds are applicable to *N*-aryl-*N*-nitrosohydroxylamine ammonium salts bearing various substituents. They include an electron-donating or -withdrawing group, such as Me, OPh, F, and Cl (Scheme 1). When

Table 1. Thermal Coupling of *N*-Nitroso-*N*-phenylhydroxylamine Ammonium Salt (1a) to Give Azoxybenzene (2a) in Various Solvents.

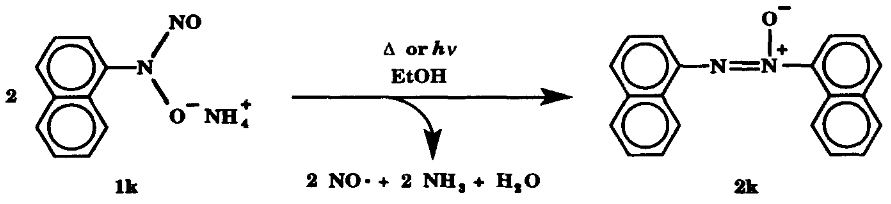
solvent	solubility (g) in 100 g of solvent at 25 °C	boiling point	yield (%)
acetone	0.212	56	25
acetonitrile	0.337	82	43
benzene	insoluble	80	22
N,*N*-dimethylformamide	16.8	153	82
ethanol	4.22	78	85
ethyl acetate	0.481	77	54
n-hexane	insoluble	69	15
tetrahydrofuran	0.172	66	34
water	12.5	100	71

the *N*-nitrosohydroxylamino groups were attached to the ortho positions of biphenyl compounds, such as in **1l** and **1m**, central heterocyclic rings were established in azoxy products through intramolecular cyclization (Scheme 2).

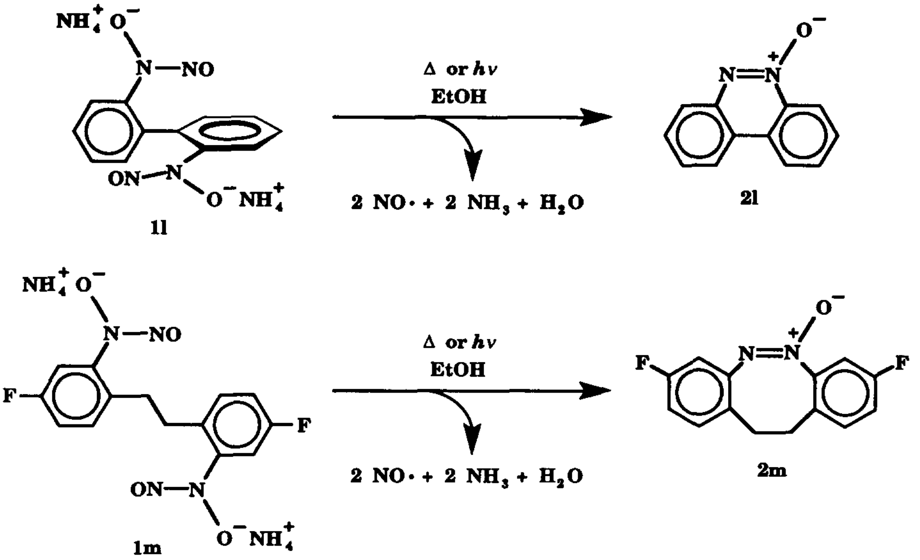
Scheme 1



a. X = H, Y = H
b. X = 4-OPh, Y = H
c. X = 4-Me, Y = H
d. X = 3-F, Y = H
e. X = 4-F, Y = H
f. X = 4-F, Y = 2-Me
g. X = 5-F, Y = 2-Me
h. X = 2-F, Y = 4-F
i. X = 4-Cl, Y = H
j. X = 3-Cl, Y = 5-Cl



Scheme 2



1l 21 1m 2m

Table 2. Thermal- and Photo-induced Coupling[a] of *N*-Aryl-*N*-nitrosohydroxylamine Ammonium Salts (1)[b] to Azoxy Compounds (2).[b]

N-aryl-*N*-nitrosohydroxylamine ammonium salt	azoxy compound	yield (%) heat	yield (%) UV
1a	**2a**[c,11]	85	58
1b	**2b**[c,11]	86	62
1c	**2c**[c,11]	91	52
1d	**2d**[c,11]	90	65
1e	**2e**[c,11]	93	70
1f	**2f**[c,11]	86	64
1g	**2g**	89	55
1h	**2h**[c,11]	87	66
1i	**2i**[c,11]	88	52
1j	**2j**[c,11]	92	51
1k	**2k**[c,11]	85	57
1l	**2l**[c,11]	80	72
1m	**2m**	92	71

[a] The reactions were carried out in ethanol by heating at 78 °C for 2.0 h or by irradiation with 450-W medium-pressure mercury UV lamp in ethanol at room temperature for 2.0 h.

[b] New compounds except labeled otherwise; fully characterized by spectroscopic methods and elemental analyses.

[c] Known compounds

Four characteristics are associated with these new coupling reactions. First, they can be performed in various organic solvents and water (see Table 1). Second, it is unnecessary to exclude moisture or oxygen gas from the reaction media. Third, the manipulation involved is simple and straightforward. Fourth, they often provide the desired products in good to excellent yields.

A new transformation of *N*-aryl-*N*-nitrosohydroxylamine ammonium salts to azoxy compounds has been established through pyrolysis or photolysis. Because the radical species NO· are generated, these thermal- and photo-induced chemical processes could be applied to DNA cleavages under controllable conditions. To develop *N*-aryl-*N*-nitrosohydroxylamine ammonium salts as DNA-cleaving agents is reported in due course.

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