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Thermolysis of 2-azido-3-(R-anilino)-1,4-naphthoquinones. Nitrene insertion versus hydrogen abstraction.

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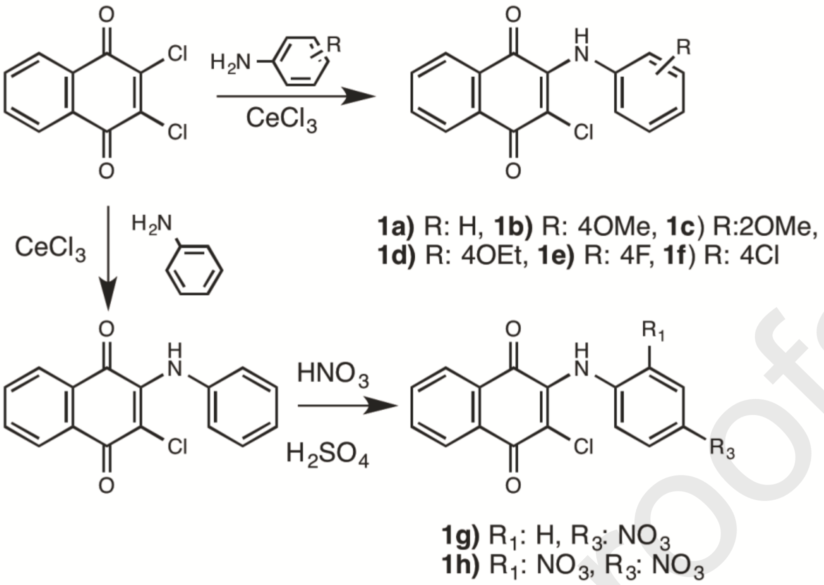
Abstract

2-chloro-3-(R-anilino)-1,4-naphthoquinones react with sodium azide upon refluxing in DMF. The thermochemistry of 2-azido-3-(R-anilino)-1,4-naphthoquinone is strongly modified by the substituent on aniline. Having an strong electron-donor like O-R results in the generation of a phenazine while having an electron-withdrawing substituent results in the formation of 2-amino-3-(R-anilino)-1,4-naphthoquinone. The products obtained are explained in terms of singlet and/or triplet nitrene chemistry.

Naphthoquinone derivatives in general, and those possessing an amino group in the two position in particular, have been the subject of intensive research. Many of these compounds find use in a variety of medicinal and biological applications. They can act as antibacterial, antimalarial and antitumor agents, as well as larvicides, herbicides and fungicides [1].

In the course of our research work on the synthesis and characterization of novel amino naphthoquinone derivatives [1], we synthesized several 2-chloro-3-(R-anilino)-1, 4-naphthoquinones **1a-h** and investigated their reactions with sodium azide. First, all compounds **1a-h** were prepared following procedures previously reported [1, 2]. Most of these derivatives can be easily obtained through a nucleophilic substitution reacting an aniline with napththoquinone using $CeCl_3$ as catalyst (Scheme 1, Table 1). Addition of catalyst induces the formation of complex between C=O and Ce, thus a selective nucleophilic substitution takes place with the replacement of a chlorine atom by a substituted aniline [1, 2]. This reaction gives good yields of R-anilino derivatives **1a-1f** where the aniline contains substituents such as H, O-R, F or Cl. However, nitroanilino derivatives where the aniline contains one or two strong electron attracting substituents are prepared by direct nitration of 2-chloro-3-anilino-1,4-naphthoquinone [1c]. All the aniline compounds were characterized by melting point, UV-Vis, IR, ^1H NMR and MS. The complete preparation and characterization data is presented in the supporting information.



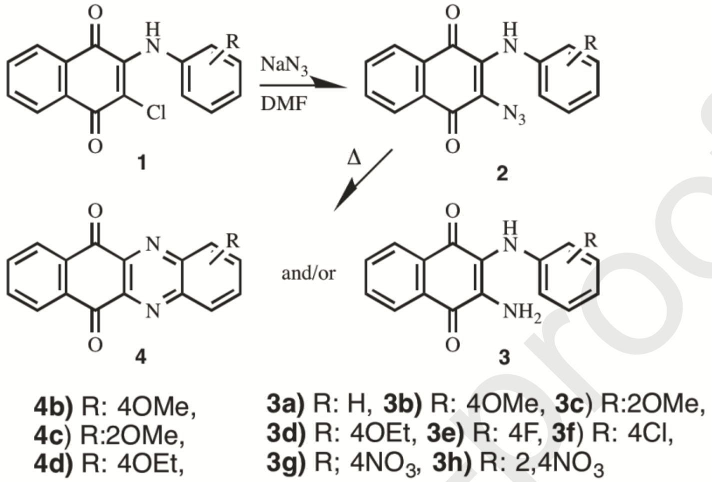
Scheme 1. Preparation of 2-chloro-3-(R-anilino)-1,4-naphthoquinone derivatives

Table 1. Yields of 2-chloro-3-(R-anilino)-1,4-naphthoquinone generated in the reaction of 1,4-naphthoquinone with substituted anilines

Compound **1**	Substituent	(% Yield)
1a	H	91
1b	4-MeO	88
1c	2-MeO	75
1d	4-EtO	90
1e	4-F	95
1f	4-Cl	72
1g	4-NO_2	65
1h	2, 4-NO_2	76

The reaction of 2-chloro-3-(R-anilino)-1,4-naphthoquinone derivatives with sodium azide to give heterocyclic phenazines and 2-amino derivatives was first reported in the literature in 1963 [3a]. In recent years, this procedure has been applied to the preparation of some naphthoquinone derivatives to investigate several biological properties [3b, 3c]. However, no mechanistic discussion has been presented to explain the products obtained in this particular reaction.

In this study, the reaction of each compound **1a-h** with sodium azide in refluxing DMF was performed. Interestingly, analysis of the reaction mixtures indicated that no azide groups were present, instead amino **3a-h** and heterocyclic **4b-d** naphthoquinone derivatives were produced **(Scheme 2, Table 2).** Since this methodology is not new, some of the compounds have been previously prepared [1, 3]. All the compounds obtained were purified and characterized by melting point, UV-Vis, IR, ^{1}H NMR, ^{13}C NMR and MS. The complete preparation and characterization data is presented in the supporting information.



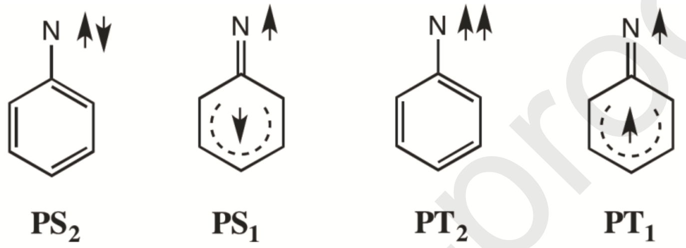
Scheme 2. Products generated in the reaction of 2-chloro-3-(R-anilino)-1,4-naphthoquinones with NaN$_3$

Table 2. Yields of products generated in the reaction 2-chloro-3-(R-anilino)-1,4-naphthoquinones with NaN$_3$

Compound **1**	Substituent	Compound **3** (% Yield)	Compound **4** (% Yield)
1a	H	81	-
1b	4-MeO	19	70
1c	2-MeO	20	75
1d	4-EtO	21	70
1e	4-F	70	-
1f	4-Cl	75	-
1g	4-NO$_2$	75	-
1h	2, 4-NO$_2$	76	-

To explain the formation of the compounds so produced, putative vinyl azides **2a-h** are proposed **(Scheme 2).** In general, vinyl azides are very reactive intermediates and generate nitrogen heterocycles such as azirines [4a]. However, recent experimental and theoretical studies by Gudmundsdottir and collaborators [4b] have indicated that 2-azido naphthoquinone does not react like a classical vinyl azide, instead it reacts in a manner similar to the structurally related aryl azides [5].

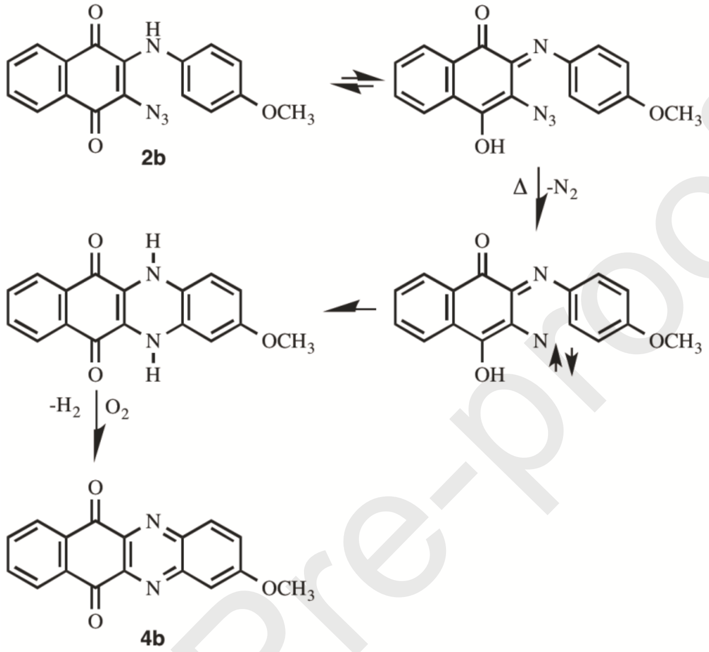
In the latter compounds, an intermediate aryl nitrene is generated upon photolysis or thermolysis [5]. Based on Wasserman's observations [6], the physical and chemical properties of aryl nitrenes have been explained in terms of singlet and triplet nitrene intermediates **(Scheme 3)** [7]. According to theory, the lowest singlet state $\mathbf{PS_1}$ has an open-shell electronic configuration with one unpaired electron on nitrogen in conjugation with the π-system of the phenyl ring, resulting in a strong stabilization. However, due to a reduced Coulomb electron-electron repulsion, a triplet nitrene $\mathbf{PT_1}$ with an open-shell configuration should be even lower in energy [8].



Scheme 3. Intermediates generated in the photochemistry of aryl azides

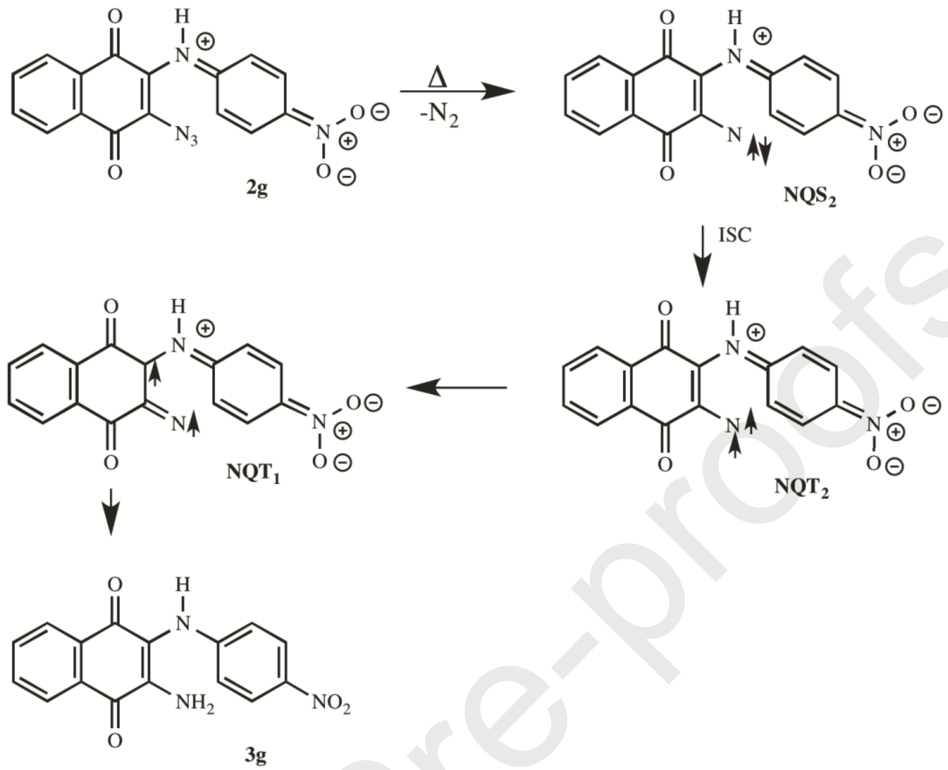
More recently, Chapyshev et al. [9] have presented some basic aspects about the structure and reactivity of aryl nitrenes. They investigated the photochemistry of several azido pyridines and explained substituent effects on the intermediate aryl nitrene structures. Several ESR studies on pyridinyl azides provided strong evidence for the existence of two triplet nitrenes with different hybridization demonstrating the existence of closed- and open-shell structures. Furthermore, Chapyshev et al. also explained the effect of neighboring nitrogen atoms with small size and poor spin holding properties, resulting in an elongation of the nitrene C-N bond thus leading to a higher reactivity of an aryl nitrene.

Several studies on the structure of 2-anilino-1,4-naphthoquinones have indicated that some of these compounds undergo a tautomeric equilibrium with two dimorphic structures [10]. This equilibrium must be particularly strong in an aniline containing electron donating groups like O-R where the anilino-nitrogen interacts strongly with the naphthoquinone ring **(Scheme 4).** Thermolysis of a vinyl azide generates a singlet nitrene [5] but according to Chapyshev et al. [9], this nitrene is strongly localized and easily undergoes C-H insertion reaction to give mostly an heterocyclic compound **4b**.



Scheme 4. Mechanism for the generation of phenazine **4b**

Very different reactivity is observed in the case of a naphthoquinone azide containing aniline or an aniline bearing electron-withdrawing groups like F, Cl or NO_2. In this case, 2-amino-3-(R-anilino)-1,4-naphthoquinone derivatives are predominantly generated. Thus, the mechanism proposed for the photochemical reaction of parent naphthoquinone azide [4b] is the same mechanism **(Scheme 5)** operating for the thermochemical reaction of **2a** and **2e-2h**. Heating, 2-chloro-3-(4-nitroaniline)-1,4-naphthoquinone **1g** with sodium azide generates azide **2g** then a singlet excited state **NQS_2**. This intermediate could undergo intersystem crossing to its triplet excited state **NQT_2** which would rapidly relax to lower energy open shell nitrene **NQT_1**. The calculated spin density for triplet phenyl and triplet naphthoquinone indicates that this latter nitrene has a strong 1,3-biradical character [4b].



Scheme 5. Mechanism for the generation of 2-amino-3-(4-nitrophenyl)-1,4-naphthoquinone

In conclusion, the thermochemistry of 2-azido-3-(R-anilino)-1,4-naphthoquinone is strongly modified by the aniline substituent. Having a strong electron-donor like O-R results in the generation of a highly reactive singlet nitrene which undergoes insertion to give a tetracyclic compound. In contrast, having an electron-withdrawing substituent favors the generation of an open-shell nitrene with a strong biradical character which undergoes hydrogen abstraction to give an amino naphthoquinone.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data with experimental procedure and characterization data is given in the supporting information.

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Highlights

_ 2-chloro-3-(R-anilino)-1,4-naphthoquinones react with sodium azide in refluxing DMF

_ 2-azido-3-(R-anilino)-1,4-naphthoquinone thermochemistry changes with substituent

_ Having an strong electron-donor like O-R results in the generation of a phenazine.

_ An electron-withdrawing substituent results in the formation of a 2-amino derivative

_ Products obtained are explained in terms of singlet or triplet nitrene chemistry.