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Amination of Naphthoquinones with Azidotrimethylsilane

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A new method for the synthesis of aminonaphthoquinones from 1,2- or 1,4-naphthoquinones and azidotrimethylsilane is described. In a similar manner 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone was transformed into 2-amino-3-hydroxy-1,4-naphthoquinone. The mechanism of these transformations and the formation of by-products are discussed.

(Keywords: Amination with direct amino group introduction; Amino-naphthoquinones)

Aminierung von Naphthochinonen mit Azidotrimethylsilan

Eine neue Methode zur Herstellung von Aminonaphthochinonen aus 1,2- oder 1,4-Naphthochinonen und Azidotrimethylsilan wird beschrieben. In analoger Weise wurde 2,3-Epoxy-2,3-dihydro-1,4-naphthochinon in 2-Amino-3-hydroxy-1,4-naphthochinon umgewandelt. Eine mechanistische Deutung dieser Umsetzung und die Bildung von Nebenprodukten wird diskutiert.

Introduction

Among several general methods for the preparation of aminonaphthoquinones the most used are oxidations of the corresponding aminonaphthalenes or amino-hydroxy-naphthoquinones, replacement of halogens of alkylthio groups in naphthoquinones, addition of amines to naphthoquinones or reduction of the corresponding azidonaphthoquinones [1]. For example, 2-aminonaphthoquinone has been prepared from 2-benzenesulfonylaminonaphthalene by oxidation and subsequent removal of the protecting group [2] or from 1,4-naphthoquinone and hydrazoic acid [3].

Results and Discussion

Naphthoquinones react with an equivalent amount of azidotrimethylsilane under relatively mild conditions to give the corresponding aminonaphthoquinones, the amine group being introduced in the quinone part of the molecule. Apparently, the solvent which is used in this transformation can influence the outcome of the reaction either in the sense of yield or formation of other products. We have found that either dimethyl sulfoxide or N,N-dimethylformamide are best solvents and the synthesis of 2-aminonaphthoquinone from azidotrimethylsilane and 1,4-naphthoquinone under various reaction conditions is presented in Table 1.

Table 1. *Syntheses of 2-aminonaphthoquinone under various reaction conditions*

Solvent	Reaction time (h)	Reaction temperature (°C)	Yield (%)	By-products
Ethanol	42	room temp.	76	
Ethanol	1	reflux	19	[a]
Ethanol	8 + 12	reflux room temp.	46	1.6% *BNQ*[b]
Triethylamine	2	80	49	11% **8**
Triethylamine	7	room temp.	56	4% **8**
N,N-Dimethylformamide + 5% triethylamine	20	room temp.	59	
N,N-Dimethylformamide	2 + 12	80 room temp.	80	
Dimethyl sulfoxide	1	80	35	2% **8**
Dimethyl sulfoxide	12	room temp.	89	

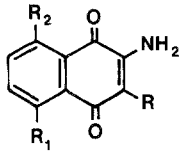
[a] Starting material was recovered in 41% yield

[b] *BNQ*: 2,2′-Binaphtho-1,2′,4,4′-quinone, m.p. 270 °C, Ref. [4, 5] gives m.p. 270–275 °C

By monitoring this transformation by means of nmr in dimethyl sulfoxide as solvent and at room temperature, we could find that 2-amino-1,4-naphthoquinone is formed rapidly. After 2 minutes this compound is present already in appreciable amount and after 8 minutes at 80 °C the starting compound has disappeared almost completely. It is also of interest to note that the dark azo compound of low solubility is formed in some reactions as by-product and its formation will be explained later when discussing the reaction mechanism. It should be mentioned that 2-amino-1,4-naphthoquinone does not react in the anticipated way with diethyl ethoxymethylenemalonate as amines generally do. The reaction was successful only after reduction of the quinone into the hydroquinone [6]. We have found, however, that the above mentioned amino compound

reacted easily with N,N-dimethylformamide dimethyl acetal to give the corresponding imine in good yield.

2-Methyl-1,4-naphthoquinone reacted in a similar manner giving the 3-amino derivative in good yield. No reaction took place in dichloromethane at room temperature or even in ethanol under reflux after 5



1: R = R_1 = R_2 = H

2: R = Me, R_1 = R_2 = H

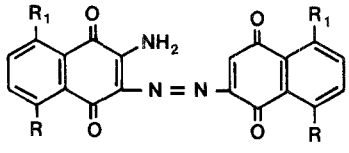
3: R = R_1 = H, R_2 = OH

4: R = R_2 = H, R_1 = OMe

5: R = R_1 = H, R_2 = OMe

6: R = H, R_1 = R_2 = OCOMe

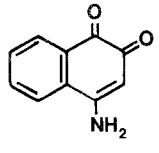
7: R = OH, R_1 = R_2 = H



8: R = R_1 = H

9: R = OMe, R_1 = H

10: R = R_1 = OCOMe



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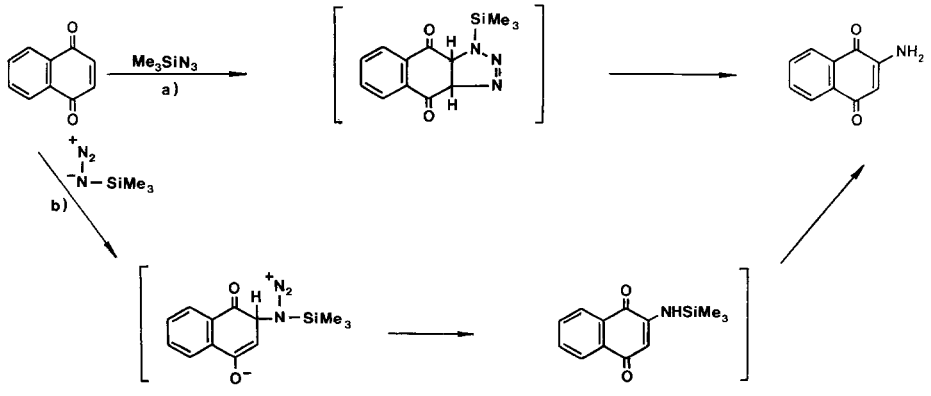
hours. 5-Hydroxy-1,4-naphthoquinone (juglone) afforded at room temperature a compound with m.p. 248–251 °C which was identified as the 3-amino isomer. On the other hand, 5-methoxy-1,4-naphthoquinone was transformed at 80 °C after 3 hours into a mixture of 6 compounds as shown by TLC. The product of low solubility, an azo-compound (**9**) was filtered and after crystallization from benzene the 3-amino isomer (**5**) was isolated. After column chromatography of the residue on silica the 2-amino isomer was obtained. To this isomer the structure of the 3-amino isomer was incorrectly assigned [7, 8]. We have obtained both isomers, 2- and 3-amino, in a ratio of about 1 : 2.2, whereas in the azide addition the 2- and 3-amino isomers were obtained in a ratio of 4 : 1 [7]. 5,8-Diacetoxy-1,4-naphthoquinone gave the 2-amino derivative in moderate yield, again accompanied with about 5% of the by-product **10**.

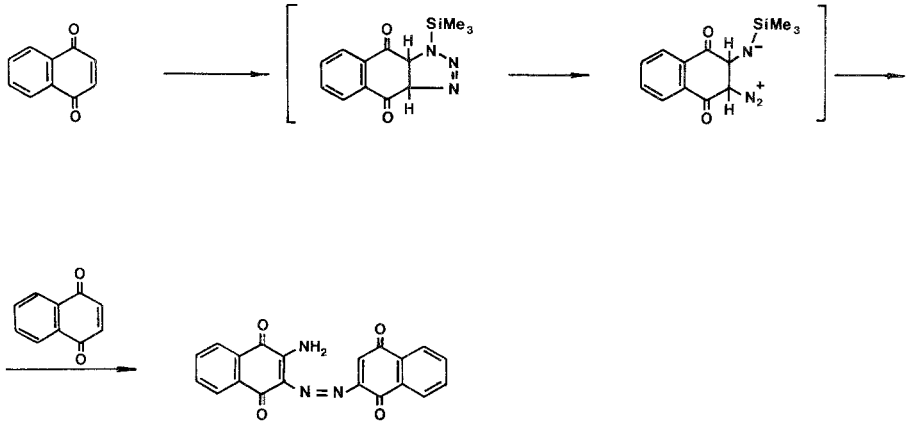
1,2-Naphthoquinone could react with azidotrimethylsilane to give either the 3-amino or 4-amino isomer. The former has been isolated so far only in an acylated form and our product was identified as 4-amino isomer (**11**). We have been able to obtain 2-amino-3-hydroxy-1,4-naphthoquinone (**7**) in good yield from the reaction between 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone and azidotrimethylsilane in warm N,N-dimethylformamide. The product was identical with the 2-amino-3-hydroxy compound obtained by reduction of 2-hydroxy-3-nitro-1,4-naphthoquinone [9] although previous reports from the literature concerning the same method of preparation give m.p. much lower, i.e. 130–140 °C [10] and above 100 °C [11], respectively. All these experiments show that aminonaphthoquinones are readily prepared by this method which is advatageous to some other, in particular those which employ either hydrazoic acid or potentially explosive azidonaphthoquinones.

Scheme 1



For the formation of aminonaphthoquinones several mechanistic pathways can be envisaged (Scheme 1). The most plausible one involves a dipolar 1,3-cycloaddition (path a) with subsequent decomposition of the intermediate fused triazoline as outlined. Although triazolines are readily formed in cycloaddition reaction of azides to compounds with carbon-carbon double bonds [12] there are only few reports of syntheses of triazolo-1,4-naphthoquinones [13–15]. These preparations require, however, either UV irradiation or they must be performed under pressure, most probably to induce dehydrogenation of the intermediate unstable triazolines to triazoles. Another variant (path b) would involve a nucleophilic attack of the corresponding azide to the quinone part, which can be regarded as a conjugated ketone and the reaction as a *Michael* type addition. The final result, i.e. the formation of the aminonaphthoquinone would be the same. We have already mentioned before that in some cases by-products were formed and analyzing for compounds containing two naphthalene parts and three nitrogen atoms (compounds **8**, **9**, and **10**). The formation of these by-products can be envisaged to result via a fused triazoline system which undergoes a N-N bond fission and the resulting diazonium salt undergoes subsequent coupling to the starting naphthoquinone (Scheme 2). Coupling of diazonium salts to quinones is a well established reaction [1]. In favour of such an intermediate is also the observation that in the case of 2-methyl-1,4-naphthoquinone such by-product was not formed since a compound of a structure similar to **8**–**10** could not be formed.

Scheme 2



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Experimental

Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^{1}H NMR spectra were recorded on a JEOL JNM C-60HL spectrometer (*TMS* as internal standard, δ values in ppm) and mass spectra were recorded on a Hitachi-

Perkin-Elmer RMU-6L spectrometer or high resolution mass spectra were recorded on a CEC-20-110C instrument. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240C CHN analyzer.

2-Amino-1,4-naphthoquinone (**1**)

A mixture of 1.58 g of 1,4-naphthoquinone and 1.15 g of azidotrimethylsilane in 15 ml of dimethyl sulfoxide was left to stand for 12 h at room temperature. The brownish red solution was diluted with water and the separated red product was filtered and crystallized from ethanol (1.41 g, 81%), m.p. 202–204 °C (Ref. [3] gives m.p. 206–208 °C). NMR (*DMSO-d_6*): 6.20 (s, H_3), 7.66–8.03 (m, 4H, *Ar*).

$C_{10}H_7NO_2$ (173.17). Calcd. C 69.36 H 4.07 N 8.09.
Found C 69.24 H 4.07 N 8.29.

The compound, when treated with an equivalent amount of N,N-dimethylformamide dimethyl acetal in boiling tetrahydrofuran for 30 min, afforded 2-(N,N-dimethylaminomethyleneamino)-1,4-naphthoquinone in almost quantitative yield. The compound was crystallized from cyclohexane, m.p. 110 °C.

$C_{13}H_{12}N_2O_2$ (228.25). Calcd. C 68.41 H 5.30 N 12.27.
Found C 67.98 H 5.44 N 12.26.

If the above experiment for the synthesis of the amino compound was performed in the same solvent at 80 °C for 1 h, the solvent evaporated in vacuo almost to dryness and benzene added, a small amount of insoluble material (2% yield) was obtained. The product was crystallized from either pyridine or a mixture of methanol and N,N-dimethylformamide to give compound **8**, m.p. 272–280 °C (dec.), MS (*m/e*): 357 (M^+).

$C_{20}H_{11}N_3O_4$ (375.32). Calcd. C 67.22 H 3.10 N 11.76.
Found C 67.55 H 3.40 N 12.08.

The same by-product was obtained in 4% or 11% yield if the reaction was performed in triethylamine at room temperature or at 80 °C, respectively.

2-Amino-3-methyl-1,4-naphthoquinone (**2**)

The compound was obtained in a similar manner as described above in 70% yield, m.p. 165 °C (Ref. [16] gives m.p. 167 °C) (from aqueous methanol).

$C_{11}H_9NO_2$ (187.13). Calcd. C 70.58 H 4.85 N 7.48.
Found C 70.22 H 4.93 N 7.49.

2-Amino-8-hydroxy-1,4-naphthoquinone (or 3-amino-5-hydroxy-1,4-naphthoquinone (**3**)

The reaction was performed in N,N-dimethylformamide as solvent and a few drops of triethylamine were added. The mixture was left to stand at room temperature for 1 h and after addition of water the product separated (yield 91%). The product was crystallized from benzene with addition of some hexane, m.p. 248–251 °C (Ref. [7] gives m.p. 251–253 °C).

$C_{10}H_7NO_3$ (189.17). Calcd. C 63.49 H 3.73 N 7.41.
Found C 63.91 H 3.83 N 7.31.

Reaction of 5-Methoxy-1,4-naphthoquinone with Azidotrimethylsilane

To a solution of 3.2 g of 5-methoxy-1,4-naphthoquinone [17] in 43 ml of N,N-dimethylformamide 2.35 g of azidotrimethylsilane was added and the mixture was stirred at 80 °C for 3 h. The solvent was evaporated and a TLC analysis (Silica, chloroform : methanol 10 : 1) of the crude product revealed the presence of 6 compounds. The product was treated with boiling ethanol, the insoluble part filtered and the residue evaporated in vacuo. The residual oily product was treated with 200 ml of boiling benzene. The insoluble part was collected (253 mg), treated with hot ethanol and crystallized from N,N-dimethylformamide with addition of methanol, m.p. 215–219 °C (compound **9**). MS (*m/e*): 417 (M^+).

$C_{22}H_{15}N_3O_6$ (417.37). Calcd. C 63.31 H 3.60 N 10.07.
Found C 63.04 H 3.51 N 9.76.

The benzene filtrate was evaporated to half of its volume and the separated crystals were filtered. After several crystallizations from the same solvent a pure compound was obtained, m.p. 226–228 °C, identified as compound **5** (3-amino-5-methoxy- or 2-amino-8-methoxy-1,4-naphthoquinone). MS (*m/e*): 203 (M^+).

$C_{11}H_9NO_3$ (203). Calcd. C 65.02 H 4.43 N 6.89.
Found C 65.44 H 4.68 N 6.63.

The benzene filtrate was evaporated to dryness and separation of the other isomer was effected by column chromatography, using silica as solid support. 1.6 g of the mixture was eluted with chloroform and fractions were tested by TLC for purity. The fraction of 1 940–2 100 ml contained the pure 2-amino isomer **4** which was crystallized from benzene (298 mg), m.p. 160 °C (Ref. [7] gives m.p. 157–158 °C). MS (*m/e*): 203 (M^+). NMR (*DMSO-d_6*): 3.82 (s, O*Me*), 5.64 (s, H_3), 6.60 (s, NH_2), 7.27–7.62 (m, H_6, H_7, H_8).

$C_{11}H_9NO_3$ (203.19). Calcd. C 65.02 H 4.43 N 6.89.
Found C 64.91 H 4.56 N 6.46.

2-Amino-5,8-diacetoxy-1,4-naphthoquinone (**6**)

To a mixture of 4.66 g of 5,8-diacetoxy-1,4-naphthoquinone [18] in 43 ml of N,N-dimethylformamide 2.35 g of azidotrimethylsilane was added and the mixture was heated at 80 °C for 3 h. The solvent was evaporated in vacuo and the residue was crystallized from ethanol to give 2.4 g of the crude product, m.p. 200–208 °C. The filtrate was evaporated to dryness and again crystallized from a small quantity of ethanol. The insoluble part had m.p. > 350 °C (252 mg) (compound **10**).

$C_{28}H_{19}N_3O_{12}$ (589.46). Calcd. C 57.05 H 3.25 N 7.13.
Found C 57.22 H 3.56 N 6.72.

The ethanolic filtrate contained some of the starting material and other products. Column chromatography on silica and elution with chloroform gave in the eluate of 1 180–1 930 ml after evaporation a residue which was crystallized from ethanol (295 mg) and identified as compound **6**, m.p. 184 °C. MS (*m/e*): 289 (M^+).

$C_{14}H_{11}NO_6$ (289.24). Calcd. C 58.13 H 3.81 N 4.84.
Found C 58.05 H 3.94 N 4.53.

4-Amino-1,2-naphthoquinone (**11**)

If a solution of 316 mg of 1,2-naphthoquinone in 5 ml of N,N-dimethylformamide was treated with 280 mg of azidotrimethylsilane, a vigorous evolution of nitrogen started. The mixture was stirred and heated at 80 °C for 1 h and the solvent was evaporated in vacuo. The residue was treated with hot pyridine, upon cooling the suspension was filtered and the solid material (283 mg) was crystallized from N,N-dimethylformamide, m.p. 295–298 °C (Ref. [3] gives m.p. 270 °C). MS (*m*/e): 173 (M^+).

$C_{10}H_7NO_2$. (173.16). Calcd. C 69.36 H 4.07 N 8.09.
Found C 69.66 H 4.24 N 8.26.

2-Amino-3-hydroxy-1,4-naphthoquinone (**7**)

A solution of 0.87 g of 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone [19] in 5 ml of N,N-dimethylformamide was treated with few drops of triethylamine and 0.6 ml of azidotrimethylsilane. Some heat was evolved and nitrogen was evolved. Upon standing at room temperature for 1 h the reaction mixture was diluted with water and the dark crystals were filtered. Upon crystallization from benzene the compound had m.p. 240–242 °C (Ref. [9] gives m.p. 242–244 °C, whereas previous reports in the literature gave a lower m.p., i.e. 130–140 °C [10] or > 100 °C [11], respectively). High resolution MS (*m*/e): 189.043, calcd. 189.043 (M^+).

$C_{10}H_7NO_3$ (189.04). Calcd. C 63.49 H 3.73 N 7.41.
Found C 63.24 H 3.77 N 7.09.

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