reactions

MDPI

Article

Various Techniques for the Synthesis of 2-Nitrophenylamino-1,4-naphthoquinone Derivatives

Elisa Leyva, Silvia E. Loredo-Carrillo * and Johana Aguilar

Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, Manuel Nava No. 6, Zona Universitaria, San Luis Potosí 78210, SLP, Mexico; elisa@uaslp.mx (E.L.); johana.aguilar@uaslp.mx (J.A.)
* Correspondence: silvia.loredo@uaslp.mx

Abstract: Nitrated products are important since they are intermediates in the synthesis of other compounds, such as explosives, perfumes, dyes and plastics, among others, and they have an easy capacity to convert into other functional groups. The synthesis of compounds with biological activity that have a nitro group in their structure is relevant to improving and/or enhancing their effect. In this work, different methodologies for the nitration of naphthoquinone derivative compounds are presented. The nitration of 3-R-2-(phenylamino)-1,4-naphthoquinone derivatives was carried out with nitric acid and sulfuric acid; milder reaction conditions were also established by diluting the acids or performing the reaction with weaker acids. Other methodologies were tested using nitrate salts for mononitrate product synthesis. We used a solvent-free reaction with oxalic acid using 3-R-2-(phenylamino)-1,4-naphthoquinones (R=H, Br or Cl), noting that the electronegativity of the chlorine group is decisive for achieving nitration with good yields. Finally, a Michael addition was performed with some nitrated anilines. To obtain denitrated compounds in the *ortho* and *para* positions, the reaction with strong acids is feasible; however, for the formation of mononitrated products, the Michael-type addition is more convenient.

Keywords: nitration; nitronium ion; Michael addition; 2-(R-phenylamino)-1,4-naphthoquinone

Citation: Leyva, E.; Loredo-Carrillo, S.E.; Aguilar, J. Various Techniques for the Synthesis of 2-Nitrophenylamino-1,4-naphthoquinone Derivatives. *Reactions* **2023**, *4*, 432–447. https://doi.org/10.3390/reactions4030026

Received: 7 June 2023
Revised: 7 July 2023
Accepted: 16 August 2023
Published: 21 August 2023

1. Introduction

Naphthoquinones are very interesting cyclic molecules; in the last few decades, they have been the center of many investigations, and they have antimicrobial, antiviral, and anticancer properties, among others.

Some naturally occurring naphthoquinones with biological activity, like plumbagin, juglone and lapachol, are synthesized by plants and have antibacterial effects. They have been used in traditional medicine of different cultures for disease treatment. For example, lapachol, present in the Biognoniacea family, is used against some types of cancer. Juglone (5-hidroxy-1,4-naphthoquinone) is obtained from the walnut (*Juglans regia* L.) tree and has antibacterial and antifungal properties. Other naphthoquinone derivatives bind to specific receptors on cancer cells, and other derivatives have been investigated for their activity against bacteria and fungi [1–9].

Plumbagin, for the genre Plumbao, is used for rheumatic pain, like antispasmodic and as an antimicrobial agent. The use of plumbagin and other naphthoquinones has recently been studied for their antioxidant and anti-inflammatory properties. These properties probably activate adaptive cellular stress response pathways as a possible neuroprotective effect [10]. In addition, plumbagin demonstrated the ability to prevent the loss of learning and memory in mice. Alzheimer's is a degenerative disease where, among other factors, there is loss of cholinergic transmission, excessive protein misfolding, and Aβ aggregation [11–14]. Naphthoquinone derivatives with hydroxyl or amino groups favor the structure–activity relationship on targets such as enzymes cholinesterase or proteins such as β-amyloid, and it is possible that naphthoquinones could contribute to a biological effect against Alzheimer's [11].

The biological activity of naphthoquinones has been attributed to several physicochemical properties. They induce oxidative stress since they cause the generation of reactive oxygen species ($O_2^{\bullet -}$, $HO^{\bullet}$, and H_2O_2). These species cause cell, enzymatic, DNA, and RNA damage, which causes cell apoptosis [1–3].

The naphthoquinone ring can undergo oxidation and reduction processes since it has the ability to accept one or two electrons and form the corresponding radical anion (Q^- or semiquinone) or dianion (Q^{2-} or hydroquinone). In an aerobic environment, a one-electron reduction could easily take place, and it is mediated by the cytochrome P4502 enzyme. For naphthoquinone to be reduced to hydroquinone (gain two electrons), an anaerobic environment is required, and the enzyme NADPH is the main species responsible for the reduction [15].

This property depends directly on its chemical structure, so it can be modified by electron-withdrawing or electron-donating groups on the quinone system and affects the oxidation and reduction processes, the biological activity, and the application of these molecules.

Different functional groups in the naphthoquinone molecule change its application. For example, derivatives of 2-hidroxy-1,4-naphthoquinones with alkyl or aminoalkyl groups present antiparasitic or anticancer activity, respectively, and 2-N,N′-dialkylamino-1,4-naphthoquinone derivatives present antileishmanicidal activity [16–18].

Quinones also present acid-base properties since they have phenolic groups in their structure, which can modify their biological activity [19]. It is possible to modulate the naphthoquinone reactivity by modifying the chemical environment, which can improve its pharmacological activity and lower adverse side effects [20,21].

Another group of interesting compounds are the amino-naphthoquinone derivatives; they are considered potential antifungal and antibacterial agents [22]. The importance in the synthesis of amino naphthoquinone derivatives lies in the fact that they are structures present in natural compounds such as quinolines and isoquinolines-5,8-diones (azonaphthoquinones), as well as in some antibiotics also of natural origin. These molecules present very diverse structures, among which the following stand out: Renierone, Mimosamicyn, Cribostatin, Streptonigrin, and Lavendermycin (Figure 1). These types of compounds present a wide range of biological activities [4,20–25].

A nitro group is a strong electron attractor; it has the ability to attract a pair of electrons, and it easily enters into resonance with aromatic electrons. Depending on the position of the nitro group, it can activate or deactivate certain positions of a given molecule, and it can also change its polarity, facilitating or inhibiting a nucleophilic addition to proteins or enzymes. Sometimes, the nitro group is not directly involved with the activity of the drug but rather affects its pharmacokinetics [26]. It has been described that the biological activity of the nitro group is due to different mechanisms; one of the most accepted is that it is reduced by generating nitroso and other superoxide species that cause cell damage [27]. The effect of a nitro group on the biological properties of a given pharmaceutical compound is very varied; it has been seen that it can have effects ranging from antibacterial, antiparasitic, antihypertensive, antineoplastic, and tranquilizer. As a consequence, there is a great interest in the investigation of methodologies to introduce this functional group [28–34].

The oxidation-reduction properties and biological activity of an anilino-naphthoquinone can be changed by modifying its structure by introducing a nitro moiety. In this work, different methodologies are proposed for the nitration of this type of quinone, where the formation of mono- or di-nitrated compounds is observed.

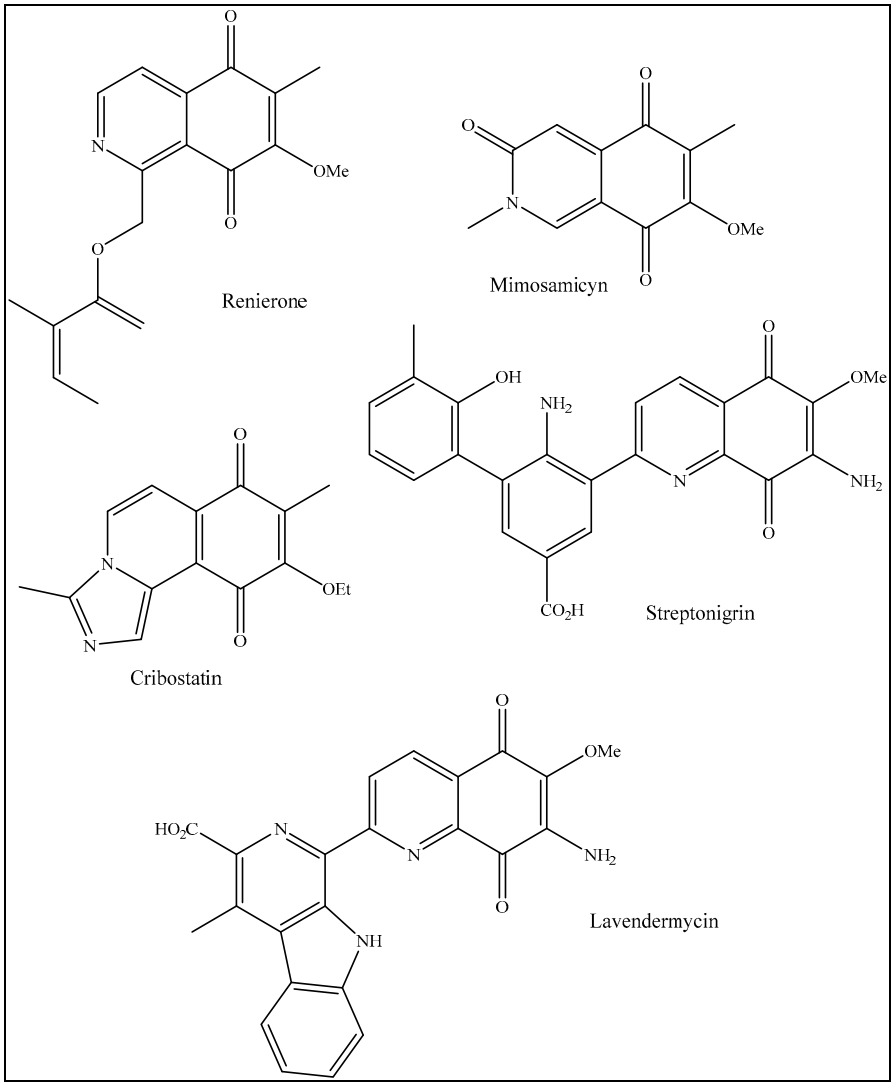


Figure 1. Natural antibiotics containing amino naphthoquinones in their structure [20–25].

2. Material and Methods

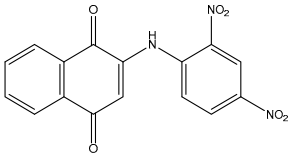
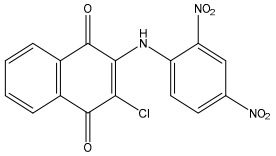
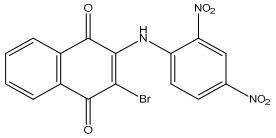
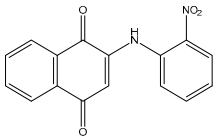
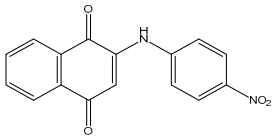
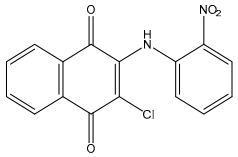
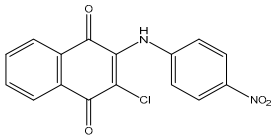
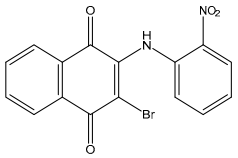
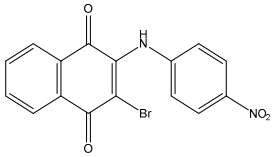
2.1. Materials and Instrumentation

Melting points were measured with a Fisher-Johns apparatus. UV-Vis Spectra were obtained on a Shimadzu UV-2401 PC spectrophotometer. IR spectra were recorded on a Nicolet IS10 Thermo Scientific FTIR spectrophotometer. NMR spectra were obtained on a Varian Mercury 400 MHz Spectrometer (the ^{1}H NMR spectrum appears in Supplementary Material) Mass spectra were recorded on a Finnigan Mat 8200 spectrometer at 70 ev. All starting compounds were purchased from commercial suppliers and were used without further purification. The reagents used were purchased from Sigma-Aldrich (St. Louis, MO, USA), and the solvents used were Fermont brand (Fermont, Fremont, OH, USA).

2.2. Different Methodologies Reported in the Literature Were Performed with Slight Modifications [35–39]

The reactions were monitored by thin-layer chromatography and allowed to react for 4–6 h; the mixture was neutralized with a 10% solution of cold sodium bicarbonate and filtered and washed with cold ethanol. The formation of precipitate was observed. The product was recrystallized several times in ethanol or $CHCl_3$. Table 1 shows different methodologies for the nitration of compounds: 1a, 1b, 1c, 2a^{1}, 2a^{2}, 2b^{1}, 2b^{2}, 2c^{1}, and 2c^{2}.

Table 1. Preparation of **1a**, **1b**, **1c**, **2a^1**, **2a^2**, **2b^1**, **2b^2**, **2c^1**, and **2c^2**.

Synthesized Compound	Reagent 0.9 mmol or 0.5 mmol	Nitration	Products (Yield%)
1a	2-(phenylamino)-1,4-naphthoquinone	7 mL H_2SO_4 conc. 1.5 mL HNO_3 conc.	 85%
1b	3-chloro-2-(phenylamino)-1,4-naphthoquinone	7 mL H_2SO_4 conc. 1.5 mL HNO_3 conc.	 90%
1c	3-bromo-2-(phenylamino)-1,4-naphthoquinone	7 mL H_2SO_4 conc. 1.5 mL HNO_3 conc.	 70%
2a^1 **2a^2**	2-(phenylamino)-1,4-naphthoquinone	7 mL H_2SO_4 conc. 1.5 mL HNO_3 conc. 3 mL of distilled H_2O or 7 mL HNO_3 conc. 3 mL of acetic acid	  60%
2b^1 **2b^2**	3-chloro-2-(phenylamino)-1,4-naphthoquinone	7 mL H_2SO_4 conc. 1.5 mL HNO_3 conc. 3 mL of distilled H_2O or 7 mL HNO_3 conc. 3 mL of acetic acid	  65%
2c^1 **2c^2**	3-bromo-2-(phenylamino)-1,4-naphthoquinone	7 mL H_2SO_4 conc. 1.5 mL HNO_3 conc. 3 mL of distilled H_2O or 7 mL HNO_3 conc. 3 mL of acetic acid	  58%

2.3. Preparation of **2a^1**, **2a^2**, **2b^1**, **2b^2**, **2c^1**, **2c^2**

Method A. Solvent-free nitration.

For this methodology, 1 mmol of 3-R-2-(phenylamino)-1,4-naphthoquinone (R= H, Cl or Br) was weighed, and 1 mmol (0.0903 g) of oxalic acid was added together with 1 mmol (0.0689 g) of $NaNO_3$; the mixture was ground until pulverized, stirred, and heated to a temperature of approximately 80 °C. The reaction was monitored by TLC and left for 6 h; the mixture was neutralized with a 10% solution of cold sodium bicarbonate and filtered and washed with cold ethanol.

Method B. Nitration with salts.

At the end of each of the methodologies described in Table 2, the mixture was neutralized with a 10% solution of cold sodium bicarbonate (the concentration of the basic solution is sufficient to neutralize the acid that remained from the reaction, so it is a moderate basic solution that does not affect the reaction), and the solution was filtered and washed with cold ethanol. Some products were recrystallized several times in ethanol or $CHCl_3$. Other products were passed through a small silica column using a mixture of hexane (30%) and ethyl acetate (70%) as the eluent solvents. It is not possible to separate the *ortho* and *para* isomers.

Table 2. Nitration with nitrated salts.

Reagent 0.5 mmol	Nitration	Products
2-(phenylamino)-1,4-naphthoquinone	2.4 or 1.2 g of Cu $(NO_3)_2$ 30 mL of anhydride acetic acid or 15 mL of carbon tetrachloride and 3.7 of acetic anhydride. The reaction mixture was allowed to stir at room temperature (25 °C) and was monitored until no starting material was observed by TLC (hexane 30% and ethyl acetate 70%) (the reaction took place for approximately one hour).	Mixture **2a^1, 2a^2**
3-chloro-2-(phenylamino)-1,4-naphthoquinone		Mixture **2b^1, 2b^2**
3-bromo-2-(phenylamino)-1,4-naphthoquinone		Mixture **2c^1, 2c^2**
2-(phenylamino)-1,4-naphthoquinone	2 g of $Ca(NO_3)_2 \bullet 4H_2O$ with 20 mL of acetic acid to dissolve the salt. The mixture was heated to 100 °C and refluxed for one hour. Subsequently, the product was precipitated by adding water.	Mixture **2a^1, 2a^2**
3-chloro-2-(phenylamino)-1,4-naphthoquinone		Mixture **2b^1, 2b^2**
3-bromo-2-(phenylamino)-1,4-naphthoquinone		Mixture **2c^1, 2c^2**

2.4. Preparation of Nitro-Phenylamino Naphthoquinone Derivatives **2a^1**, **2a^2**, **3a^1**, **3a^2**, **3a^3**, **3a^4**; *by Michael Addition to 1,4-Naphtoquinone with Nitrated Anilines*

The substituted naphthoquinones were prepared by the method reported in the literature with several modifications [40,41].

1,4-Naphthoquinone (1 mmol) was dissolved in ethanol (10 mL), and Lewis acid, $CeCl_3.7H_2O$, or $FeCl_3$ (0.1 mmol, 0.372 g or 0.162 g, respectively) was added. The reaction mixture was stirred for at least 60 min. A solution of a given aniline (1 mmol, 0.09 mL) in ethanol (10 mL) was slowly added, and the mixture was allowed to react for 4 to 72 h, depending on the aniline substituent(s). The reaction vessel was equipped with a reflux condenser to minimize ethanol losses during the experiment. The reaction was monitored by TLC. The solution turned deep red or orange-yellow when the corresponding 2-(R-phenylamino)-1,4-naphthoquinone was formed. The resulting solid was filtered and washed with cold ethanol. After recrystallization from ethanol, the desired product was obtained as a pure and crystalline-colored solid.

2.5. Characterization

Characterization of **1a**: 2-(2,4-dinitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 264–266 °C. Uv-Vis (CH_3OH) λ max (nm): 265, 315, and 448. IR (ATR) (cm^{-1}), 3276 (NH), 1689, 1672 (C=O), 1500, 1339 (NO_2), 1583 (N-H

aromatic), and 1278 (C-N aromatic). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 9.04 (1H, s, NH), 8.56 (1H, d, *J* = 2.7, aromatic H), 8.23 (1H, dd, *J1* = 9.1, *J2* = 2.16, aromatic H), 8.22 (1H, dd, *J1* = 8.8, *J2* = 2.19 aromatic H), 8.15 (1H, td, *J1* = 7.52, *J2* = 2.16 aromatic H), 7.92 (1H, td, *J1* = 8.78, *J2*= 2.16, aromatic H), 7.88 (1H, dd, *J1* = 8.78, *J2* = 2.16, aromatic H), 7.82 (1H, td, *J* = 7.52, *J2* = 2.16, aromatic H), and 6.88 (1H, s, vinyl H); HRMS calcd for $C_{16}H_9N_3O_6$ was 339.0491 and found 339.0485.

Characterization of **2a[1]**: 2-(2-nitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 205–207 °C. UV–Vis (CH_3OH) λ max (nm): 269, 343, and 451. IR (ATR) (cm^{-1}), 3304 (NH), 1671, 1641 (C=O), 1500, 1337 (NO_2), 1576 (N-H aromatic), and 1278 (C-N aromatic); ^1H NMR (DMSO-d6, 400 MHz,) δ (ppm): 9.74 (1H, s, NH), 8.21 (1H, dd, *J1* = 8.21, *J2* = 1.17, aromatic H), 8.1 (1H, dd, *J1* = 8.2, *J2* = 1.17, aromatic H), 7.99 (1H, dd, *J1* = 7.8, *J2* = 1.17aromatic H), 7.91 (1H, td, *J1* = 7.42, *J2* = 1.17 aromatic H), 7.84 (1H, td, *J1* = 7.42, *J2* = 1.17 aromatic H), 7.83 (1H, dd, *J1* =6.45, *J2* = 1.56, aromatic H), 7.81 (1H, td, *J1* = 8.2, *J2* = 1.17 aromatic H), 7.45 (1H, td, *J1* = 8.2, *J2* = 1.71, aromatic H), and 6.26 (1H, s, vinyl H); HRMS calcd for $C_{16}H_{10}N_2O_4$ was 294.0641 and found 294.0635.

Characterization of **3a[1]**: 2-(3-nitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 280–286 °C. UV–Vis (CH_3OH) λ max (nm): 275, 343, and 450. IR (ATR) (cm^{-1}), 3212.33 (NH), 1675 (C=O), 1523, 1372 (NO_2), 1575.01 (N-H aromatic), and 1298.63 (C-N aromatic); ^1H NMR (DMSO-d6, 400 MHz,) δ (ppm): 9.57 (1H, s, N-H), 8.32 (2H, dd, *J1* = 7.42, *J2* = 1.37 aromatic H), 8.16 (2H, dd, *J1* = 7.42, *J2* = 1.37 aromatic H), 7.89, 7.81 (1H, td, *J1* = 7.42, *J2* = 7.42, aromatic H), 7.45 (1H, dd, *J1* = 8.21, *J2* = 1.56, aromatic H), 7.21 (3H, dd, *J1*= 8.21, *J2* = 1.56, aromatic H), and 6.51 (1H, s, vinyl H); HRMS calcd for $C_{16}H_{10}N_2O_4$ was 294.0641 and found 294.0633.

Characterization of **2a[2]**: 2-(4-nitrophenylamino)-1,4-naphthoquinone

Red solid experimental mp: 337–339 °C. Uv-Vis (CH_3OH) λ max (nm): 265, 338, and 450. IR (ATR) (cm^{-1}), 3185 (NH), 1671, 1641 (C=O), 1497, 1330 (NO_2), 1570 (N-H aromatic), and 1290 (C-N aromatic). ^1H NMR (DMSO-d6, 400 MHz,) δ (ppm): 9.56 (1H, s, NH), 8.33 (1H, dd, *J1* = 8.20, *J2* = 1.37, aromatic H), 8.17 (1H, dd, *J1* = 8.5, *J2* = 1.37aromatic H), 7.89 (1H, td, *J1* = 7.03, *J2* = 1.37, aromatic H), 7.83 (1H, td, *J* = 7.03, aromatic H), 7.46 (2H, d, *J* = 8.98 Hz, aromatic H), 7.22 (2H, d, *J* = 8.59 Hz, aromatic), and 6.53 (1H, s, vinyl H); HRMS calcd for $C_{16}H_{10}N_2O_4$ was 294.0641 and found 294.0631.

Characterization of **3a[2]**: 2-(2-fluoro-5-nitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 212–216 °C. Uv-Vis (CH_3OH) λ max (nm): 268, 345, and 435. IR (ATR) (cm^{-1}), 3180.53 (NH), 1738.67, 1681.51 (C=O), 1521.04, 1345.15 (NO_2), 1499.99 (N-H aromatic), 1304.92 (C-N aromatic), and 1243.9 (C-F). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 8.39 (1H, dd *J1* = 9.51, *J2* = 2.5, aromatic H), 8.37 (dd *J1* = 9.51, *J2* = 2.91, aromatic H), 8.16 (1H, *J1* = 8.42, *J2* = 2.8, aromatic H), 7.76, 7.74, 7.72 (2H, td, *J1* = 7.32, *J2* = 1.46, aromatic H and NH), 7.37 (1H, t, *JHF* = 5.8 aromatic H), and 6.45 (1H, s vinyl H).

Characterization of **3a[3]**: 2-(4-fluoro-3-nitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 244–248 °C. Uv-Vis (CH_3OH) λ max (nm): 272, 350, and 450. IR (ATR) (cm^{-1}), 3236.66 (NH), 1677.32 (C=O), 1574.32, 1374.32 (NO_2), 1514.71 (N-H aromatic), 11,296.84 (C-N aromatic), and 996.76 (C-F). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 9.46 (1H, s, N-H), 8.12 (H-F, dd, *J1* = 6.64, *J2* = 2.74, aromatic H), 8.06 (1H, dd, *J1* = 7.24, *J2* = 1.37.aromatic H), 7.95 (1H, dd, *J1* = 7.62, *J2* = 1.37, aromatic H), 7.86 (1H, dd, *J1* = 7.24, *J2* = 1.37 = aromatic H), 7.82 (1H, dd, *J* = 7.24, *J2* = 1.37, aromatic H), 7.80 (1H, dd, *J1* = 8.99, *J2*= 6.06, aromatic H), 7.63(H-F, td, *J1* = 8.99, *J2* = 8.99, aromatic H), and 6.21 (1H, s, vinyl H). HRMS calcd for $C_{16}H_9N_2O_6F$ was 312.02 and found 312.2.

Characterization of **3a[4]**: 2-(2-fluoro-4-nitrophenylamino)-1,4-naphthoquinone

Yellow solid experimental mp: 212–216 °C. Uv-Vis (CH_3OH) λ max (nm): 268, 350, and 435. IR (ATR) (cm^{-1}), 3180.53 (NH), 1738.67, 1681.51 (C=O), 1521.04, 1345.15 (NO_2), 1499.99 (N-H aromatic), 1304.92 (C-N aromatic), and 1243.98 (C-F). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 8.39 (1H, dd, *J1* = 9.5, *J2* = 2.5, aromatic H), 8.37 (1H, dd, *J1* = 9.5, *J2* = 2.91, aromatic H), 8.16 (H-F, t, *J1* = 9.88, *J2* = 8.42, aromatic H), 7.83 (1H, dd *J1* = 7.32, *J2* = 1.09 aromatic H), 7.80 (1H, dd *J1* = 7.32, *J2* = 1.46 aromatic H), 7.81 7.76, 7.74, 7.72 (2H, td *J1* = 7.32, 7.68,

J2 = 1.09,1.46, aromatic H and NH), 7.37 (H-F, t, *J1* = 5.85, aromatic H), and 6.45 (1H, s, vinyl H). HRMS calcd for $C_{16}H_9N_3O_6$ was 339.0491 and found 339.0485.

Characterization of **1b**: 3-chloro-2-(2,4-nitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 236–238 °C. Uv-Vis (CH_3OH) λ max (nm): 210, 230, 327, and 428. IR (ATR) (cm^{-1}), 3290.12 (NH), 1645.41 (C=O), 1527.14, 1350.37 (NO_2), 1321.88 (C-N), and 1122.09 (C-Cl). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 10.02 (1H, s, NH), 9.14 (1H, d, *J* = 2.6, aromatic H), 8.40 (1H, dd, *J1* = 9.2, *J2* = 2.6, aromatic H), 8.26 (1H, dd, *J1* = 7.5, *J2* = 1.2, aromatic H), 8.20 (1H, dd, *J1* = 7.5, *J2* = 1.3, aromatic H), 7.89–7.81 (2H, m, aromatic H), and 6.90 (1H, d, *J* = 9.2, aromatic H). HRMS calcd for $C_{16}H_9N_2O_6F$ was 373.03 and found 373.

Characterization of **2b²**: 3-chloro-2-(4-nitrophenylamino)-1,4-naphthoquinone

Orange solid experimental mp: 282–284 °C. Uv-Vis (CH_3OH) λ max (nm): 219, 270, 336, and 430. IR (ATR) (cm^{-1}), 3290.27 (NH), 1671.20 (C=O), 1518.88, 1340.84 (NO_2), 1259.09 (C-N aromatic), and 1125.68 (C-Cl). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 8.27, 814 (2H, m aromatic H), 7.83 (1H, t, *J* = 7.6, aromatic H), 7.76 (1H, t, *J* = 7.6 aromatic H), 7.71 (3H, m, aromatic H and NH), and 7.52 (2H, m, aromatic H). HRMS calcd for $C_{16}H_9N_2O_6F$ was 328.30 and found 328.

Characterization of **1c**: 3-bromo-2-(2,4-nitrophenylamino)-1,4-naphthoquinone

Red solid experimental mp: 255–260 °C. Uv-Vis (CH_3OH) λ max (nm): 260, 338, and 442. IR (ATR) (cm^{-1}), 3265.42 (NH), 1667.34, 1617.46 (C=O), 1503.24, 1351.47 (NO_2), 1255.92 (C-N), and 1064.41 (C-Br). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 9.96 (1H, s, NH), 9.15 (1H, d, *J1* = 2.56, aromatic H), 8.38, 8.35 (1H, dd, *J1* = 9.15, *J2* = 2.93, aromatic H), 8.26 (2H, dd, *J1* = 7.68, *J2* = 2.19, 1.46, aromatic H), 8.20, 8.18 (2H, dd, *J1* = 7.68, 7.32, *J2* = 1.83, 2.19, aromatic H), and 6.94 (1H, d, *J1* = 9.52).

Characterization of **2c²**: 3-bromo-2-(4-nitrophenylamino)-1,4-naphthoquinone

Red solid experimental mp: 242–247 °C. Uv-Vis (CH_3OH) λ max (nm): 242, 314, and 440. IR (ATR) (cm^{-1}), 3237.29 (NH), 1685.43, 1646.85 (C=O), 1507.72, 1335.66 (NO_2), 1253.63 (C-N), and 1056.45 (C-Br). NMR ($CDCl_3$, 400 MHz,) δ (ppm): 9.62 (1H, s, NH), 8.62 (2H, t, *J1* = 7.68, *J2* = 1.83, aromatic H), 8.18 (2H, dd, *J1* = 7.68, *J2* = 1.32. aromatic H), 8.12 (2H, dd, *J1* = 7.68, *J2* = 2.2 aromatic H), and 7.85 (2H, m, aromatic H).

3. Results and Discussion

The nitration of aromatic compounds is a very studied reaction and is highly used industrially, because nitration compounds are intermediaries for drugs, perfumes, dyes, explosives, and plastics [42]. Nitration is the addition of a nitro group to a compound. It is generally carried out by the attack of a nucleophilic molecule on the nitronium ion (NO_2^+). The reaction involves the formation of a sigma complex called the Wheland intermediate. The formation of the nitronium ion comes from the dehydration of HNO_3, which is promoted by the presence of a strong acid; the most commonly used is H_2SO_4, but other organic acids, such as acetic acid, can be included. The formation of the nitronium ion can be influenced by several factors, such as the strength and concentration of the acid and environmental factors [43]. The mononitration of benzene has an enthalpy of reaction (ΔH) of −117 kJ/mol, and that of naphthalene is −209 kJ/mol, so it is an exothermic and explosive reaction. It has been studied for the last 10 years, and the basis of the method is attributed to Ingold and Hughes [43,44].

The nitration of 3-R-2-(phenylamino)-1,4-naphthoquinone derivatives was carried out in order to introduce the nitro group in the molecule since it is known that this functional group has an important antimicrobial property. It is also possible to make a second substitution at position 3 of the naphthoquinone ring since, with the first reaction, the electrophilicity of said position is decreased due to the electronic effects of the substituents. By introducing a highly electroattracting group, position 3 recovers its electrophilicity [45–47].

The nitration reaction was carried out by the conventional method using concentrated nitric and sulfuric acids in the synthesis of nitro-phenylamino-naphthoquinone derivatives. The mechanism is represented in Figure 2. The formation of the nitronium ion comes from

the dehydration of HNO_3, which is promoted by the presence of a strong acid; in this case, H_2SO_4 was used. The nucleophilic attack subsequently comes from the aromatic ring attached to the amine. The amine electron pair injects electron density, increasing its nucleophilic capacity, while in the other ring of this molecule, the attack is less likely due to the resonance and the presence of carbonyl groups.

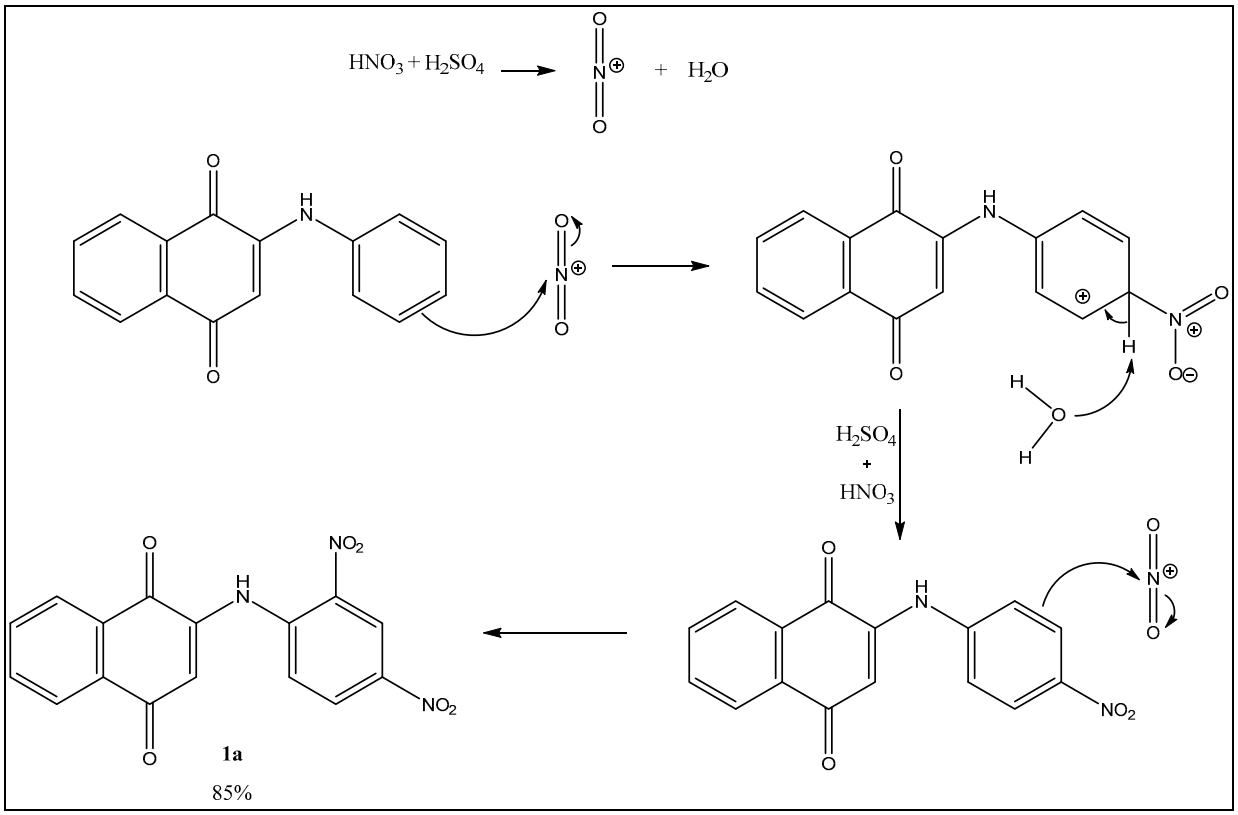


Figure 2. Mechanism classic of aromatic nitration with 1,4-naphthoquinones.

After the nucleophilic attack of aniline, naphthoquinone recovers its aromaticity by deprotonation of the ring carried out by a water molecule.

In this nitration, a single orange-colored product was formed, the *ortho–para* dinitrate compound. Regioselectivity in a reaction is governed by steric hindrance, the interaction between substituents and reactants, as well as electronic effects and solvent effects. The nitration of aromatics containing electron-donor substituents generally leads to substitution at the *ortho* and *para* positions. Bulky substituents in reactants and/or on the substrates usually lead to high concentrations of *para* products [48].

Other synthetic methodologies were carried out for the preparation of nitro-phenylamino-naphthoquinone derivatives in order to soften the reaction conditions, which would more selectively produce mononitrate derivatives since the nitronium ion concentration is lower.

One of them involved diluting the acids in water, and for the other, acetic acid was used instead of sulfuric acid. In both reactions, the presence of two products was observed. The compounds obtained were the corresponding mononitrate in the *ortho* and *para* positions (Figure 3). This was corroborated by thin-layer chromatography, observing the presence of two yellow spots of very similar polarity, that is, with a very close retention factor (Rf). They were compared with the Rf of the dinitrate compound, and it was found that it did not correspond to either of the two products (Table 3).

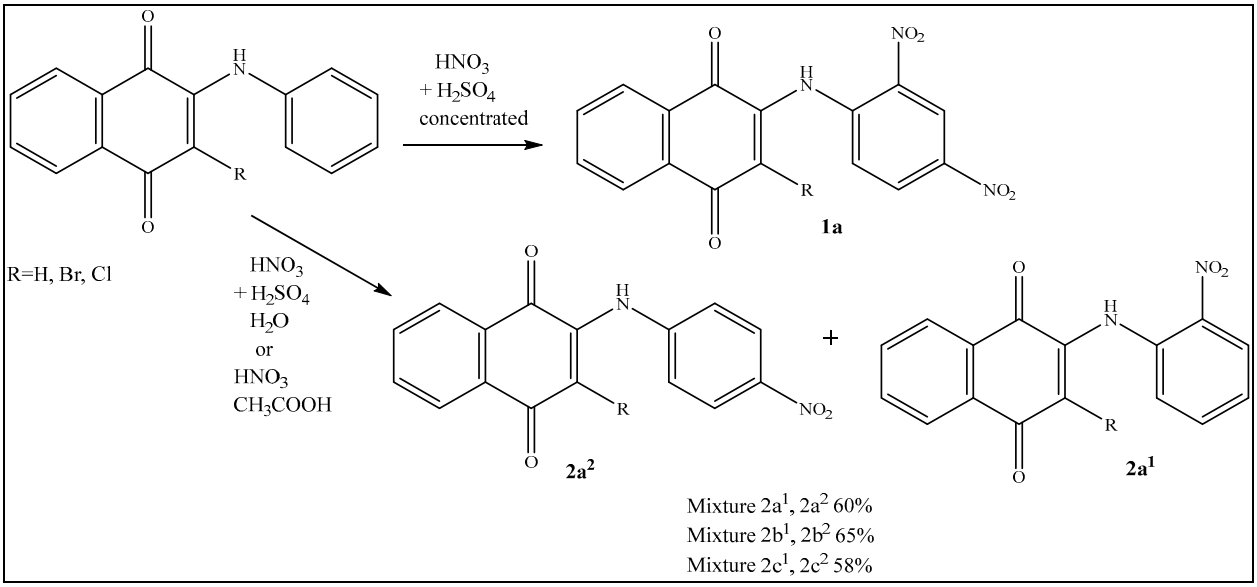


Figure 3. Di and mononitration of 3-R-(phenylamino), 1,4-naphthoquinone.

Table 3. Retention factor (Rf) for **1a**, **2a^1**, and **2a^2**.

Product	Rf	Yield (%)
1a	0.5	85
2a^1	0.42	60 (mixture)
2a^2	0.45	60 (mixture)

(Hexane 30% and ethyl acetate 70%).

Another methodology for the nitration of aromatic compounds is the use of nitronium salts, which replace the acid mixture [49]. Effective NO_2BF_4 and NO_2PF_6 have been used for substrates with electroattracting groups, and a high selectivity in these reactions was obtained. Anhydrous N_2O_5 is used, especially for compounds that are unstable in an acid medium. The use of nitrate salts to carry out the nitration of aromatic compounds has received much attention. The nitration has been carried out using $AgNO_3/BF_3$ in acetonitrile for the nitration of benzene, toluene, ethylbenzene, and *p*-xylene, among others, obtaining mixtures of isomers with excellent yields [50]. However, many of these nitrating agents require certain manipulations before they can be used, which limits the applications of some aromatic compounds.

Solvent-free reactions in organic chemistry have gained much interest in recent years, with research looking to modernize classical reactions and make them safer and easier to perform [51]. Reducing or eliminating the use of organic solvents during organic synthesis reactions leads to clean, efficient, and economical methodologies; safety is increased, work is simplified, and costs are reduced. Efficiency is increased since larger quantities of reagents can be used in the same equipment [52].

The elimination of volatile solvents has been one of the most important advances in green chemistry since these types of reactions are simple, less toxic, and not as much waste is generated, making them cleaner. A solvent-free nitration strategy was carried out using sodium nitrate salt and oxalic acid [53]. This reaction has been reported for the nitration of different phenols at room temperature under ambient conditions and microwave irradiation, achieving yields of up to 94%.

We performed the methodology described in the literature with some modifications [53]. The reaction was carried out first at room temperature and without using microwaves, failing to carry out the nitration of naphthoquinone. It was necessary to heat the reaction system to obtain the corresponding mononitrate products. The proposed mechanism for this reaction is shown in Figure 4. An interaction between the salt and

the acid is first proposed to form the nitronium ion necessary for the nitration reaction to take place. The reaction was carried out with different substituents in position 3 (chlorine, bromine, and hydrogen), achieving nitration in a significant percentage. When we had the chlorine group, a mixture of the *ortho* and *para* products (mononitrates) was only obtained with an 80% yield. However, when the bromine substituent was used, a much lower yield (30%) was achieved, still observing a lot of raw material, even leaving the reaction mixture for 8 h. In the case of 2-(phenylamino)-1,4 -naphthoquinones (PAN), the reaction does not proceed.

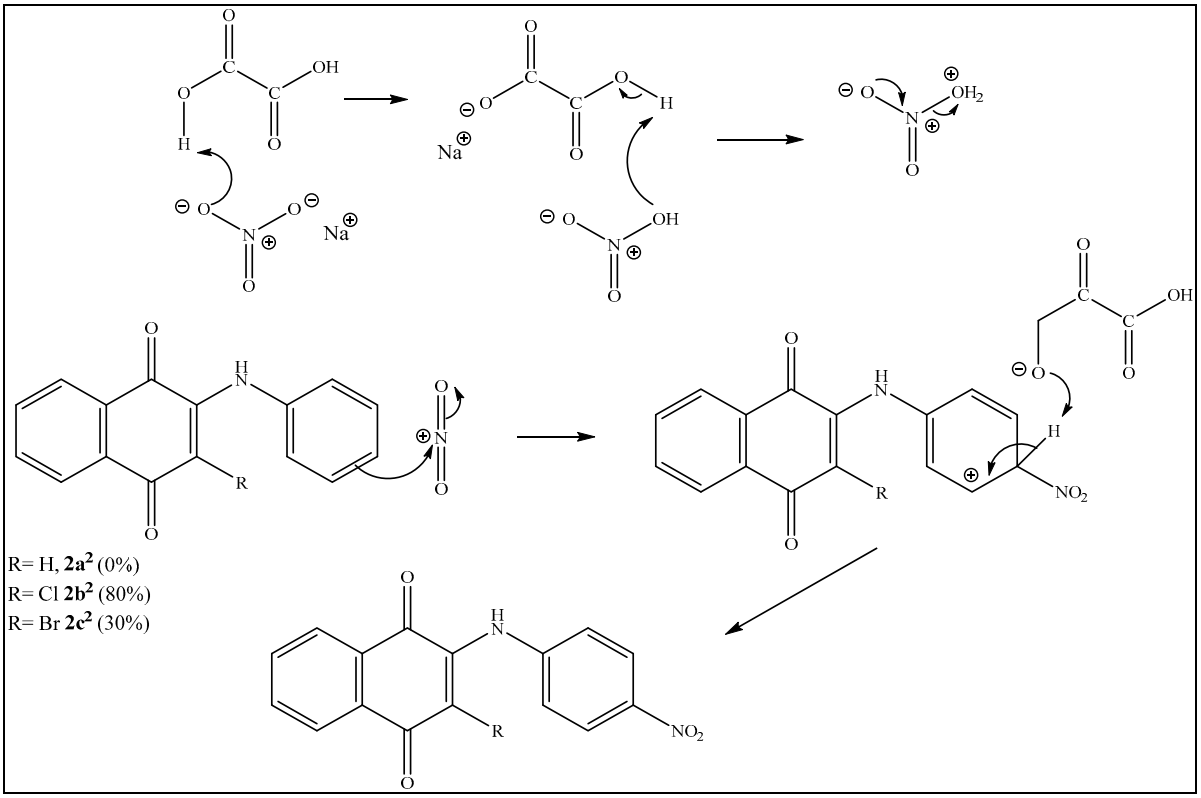


Figure 4. Solvent-free nitration of 2-anilino-1,4-naphthoquinones.

The main difference between these molecules is that chlorine is the one with the highest electronegativity, followed by bromine and hydrogen. The yields can be explained by the electronegative effect of chlorine, whereby an inductive effect gives electronic density through bonds, favoring the attack of the electron pairs of the double bonds of the aromatic compound and lowering the activation energy to obtain the products.

The reaction was also carried out using microwave radiation, leaving the reaction mixture for up to 2 h; however, the expected products were not obtained in any case. So, this system does not work in microwaves, probably due to the absence of a polar solvent that absorbs and diffuses energy efficiently.

Obtaining the nitrated products was confirmed by IR spectroscopy. Figure 5 shows the infrared spectrum for the compound 3-chloro-2(-dinitrophenylamino)-1,4-naphthoquinone, where two characteristic bands of the nitro group are shown: the first at position 1528.17 cm^{-1} corresponds to the asymmetric elongation of the nitro group, and the second at 1351.00 cm^{-1} is characteristic of the symmetric elongation of the nitro group [54].

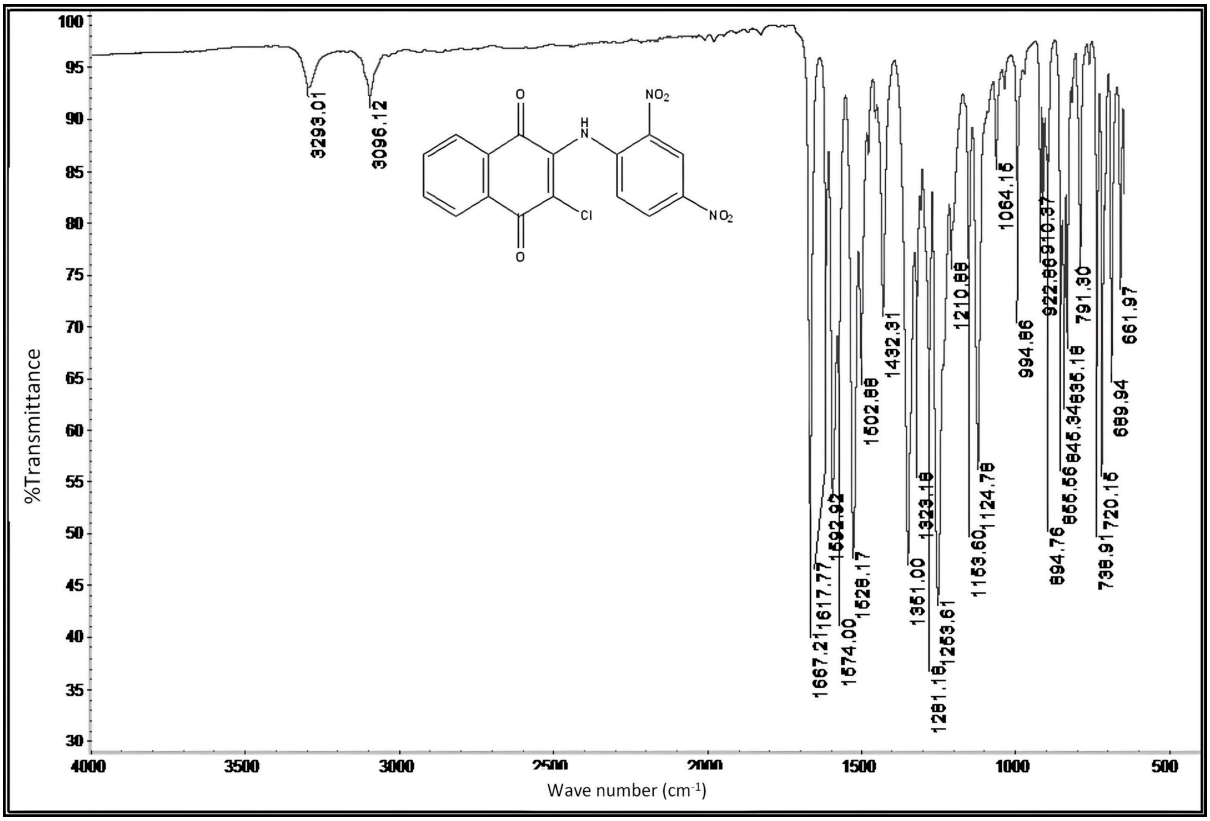


Figure 5. IR spectra of 3-chloro-2-(2,4-dinitrophenylamino)1,4-naphthoquinone.

Other nitration strategies were carried out using copper nitrate and calcium nitrate salts in order to direct the reaction to obtain a single product; the results are shown in Table 4.

Table 4. Different nitration strategies with salts of 3-R-2-(phenylamine)-1,4-naphthoquinone.

Naphthoquinone	Nitrating Reagent	Products (Yield%)
3-chloro-2-(phenylamine)-1,4-naphthoquinone	Copper Nitrate	**2a**[2] (22%)
3-bromo-2-(phenylamine)-1,4-naphthoquinone	Calcium Nitrate	**2b**[2] (18%)
2-(phenylamine)-1,4-naphthoquinone	Copper Nitrate	Several products

The mononitrate products obtained were in the *para* position; the reason why the formation of a single product is observed may be due to the steric hindrance of the salt, which, being more voluminous and having an interaction of charges with the nitronium ion, does not allow the formation of the *ortho* product, and the yields were not very high.

Further, since strong acids are not present, the exothermic reaction between nitric acid and sulfuric acid does not take place, so the reaction system does not have much heat or energy to allow the other transition states to be reached and other isomers of the products formed. For the reaction mechanism, the formation of the nitronium ion from the dehydration of the salt by acetic anhydride is proposed, and later, the attack to the ion by the ring of the anilino group and the recovery of the aromaticity by the capture of the proton by the acetic acid.

Another methodology for obtaining nitrated derivatives is to carry out the reaction of 1,4-naphthoquinone with nitrated anilines, as in Figure 6. It is difficult for an aniline attack

to take place due to the electroattracting effect of the nitro groups that limit its action as a nucleophile.

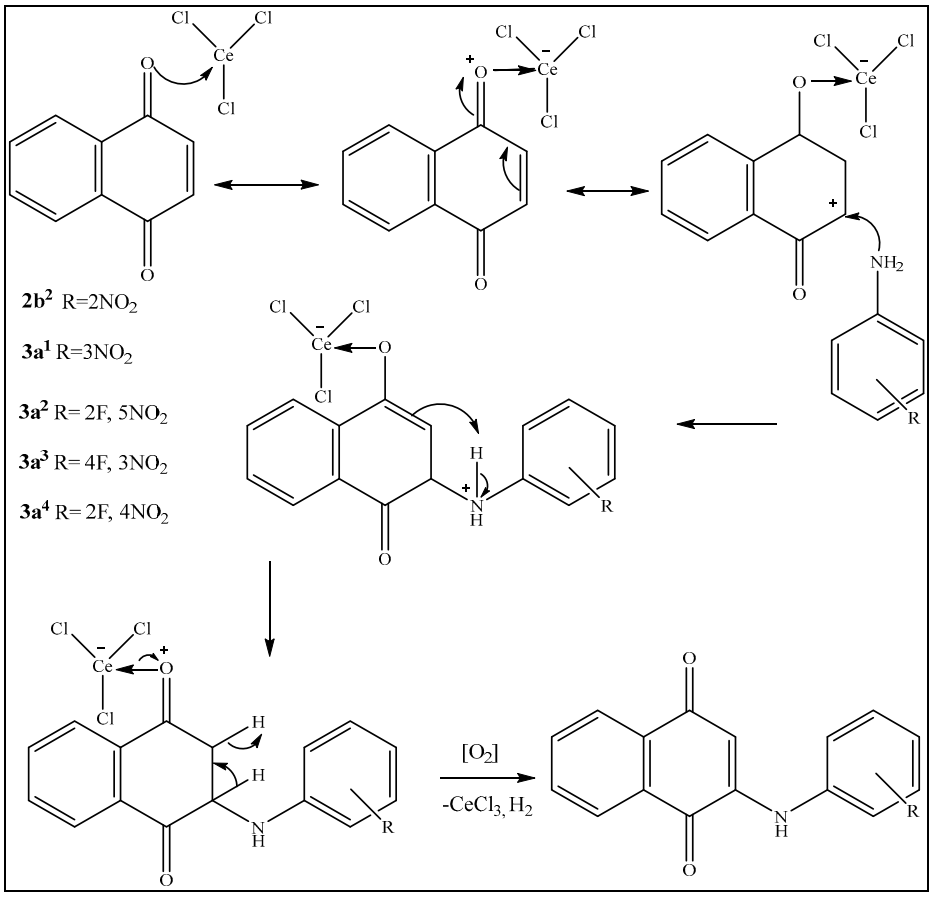


Figure 6. Michael addition with 1,4-naphthoquinone, some nitrates anilines, and a $CeCl_3$-like catalyst.

This reaction was reported using 1,4-naphthoquinone and some nitrated anilines, observing that Michael's addition is not a satisfactory methodology for obtaining nitrated derivatives, since it is observed that only traces of the product are obtained. When carrying out the reaction with 2,4-dinitroaniline, this does not proceed [55].

The Michael addition with 1,4-naphthoquinone was carried out using two types of catalysts, $FeCl_3$ and $CeCl_3$, because these are the ones that presented the best results when the reaction was carried out with other types of anilines. The reaction was carried out in ethanol at room temperature, and they were left to react for several days until a change in the system was observed. The reaction was also carried out under microwave conditions. The results are shown in Tables 5 and 6 [56,57].

Table 5. Reactions of 1,4-anilinonapthoquinone with different nitrated anilines.

Products	Yield (%)		
	Without Catalysis	$CeCl_3$	$FeCl_3$
2a^1	---	---	23.9
3a^1	13.8	77.0	73.5
2a^2	---	52.8	53.0
1a	---	---	---
3a^2	6.1	65.5	61.0
3a^3	---	70.7	51.6
3a^4	---	22.0	23.0

Table 6. Nitration of naphthoquinones in mw.

Products	Yield (%)	
	$CeCl_3$	$FeCl_3$
2a[1]	---	---
3a[1]	23.3	28.7
2a[2]	18.1	10.8
1a	---	---
3a2	35.3	30.7
3a[3]	32.3	31.6
3a[4]	---	---

As can be seen in Table 5, the results obtained show very good yields in the presence of catalysts between 50 and 77%, except for $2NO_2$PAN and 2F-$4NO_2$PAN, where yields were around 20%. For the reaction with dinitrate aniline, the reaction does not proceed since the electroattractive effect of the two nitro groups is too strong to allow the aniline electron pair to attack the naphthoquinone. However, this methodology allows the preparation of nitrated naphthoquinones and has certain advantages if we compare it with previous nitration reactions, since the desired product is obtained in a single step, and it is not necessary to use strong acids that are difficult to handle, store, and process. The disadvantage is the long reaction times.

The synthesis of $2NO_2$PAN was achieved in a very low yield of 23.9% and only with the $FeCl_3$ catalyst. The reaction does not proceed with $CeCl_3$; this may be due to the steric hindrance of the nitro group in position two of the naphthoquinone since $CeCl_3$ is a larger molecule than $FeCl_3$.

The reaction was also carried out under microwave conditions; the results are shown in Table 6. For this methodology, the same catalysts as under ambient conditions were used. The synthesis of the $2NO_2$PAN and 2F-$4NO_2$ molecules was not possible under microwave radiation [57].

The yields obtained with microwave reactions were lower than those obtained under ambient conditions. However, it must be taken into account that the reaction times were shorter, around 30 min.

The use of microwaves in this type of reaction is advantageous since the products were obtained in a few minutes, and the reaction under ambient conditions requires several days. However, some of the compounds could not be synthesized, at least in the reaction times that were established in our methodology [30].

Introducing the nitro group in the amino-naphthoquinone molecule was important because it could increase the biological activity of this type of molecule. In addition, the electroattractive effect of the nitro groups allows activating position 3 of naphthoquinone to achieve the introduction of other substituents. Since, as previously mentioned, even having good leaving groups in positions 2 and 3 (such as chlorine or bromine), it is not possible to carry out the disubstitution reaction with amines.

4. Conclusions

Phenylamino-1,4-naphthoquinone derivatives have diverse biological activity. Their biological and physicochemical properties could be modified by the introduction of a nitro substituent since this group is known to have antimicrobial activity.

Performing the nitration under conventional conditions, using concentrated H_2SO and HNO_3, gave the regioselective formation of ortho–para dinitrate phenyl amino naphthoquinone. Under milder conditions, diluting with water or using acetic acid instead of sulfuric acid, a mixture of ortho and para monosubstituted compounds was obtained. In all the cases where these monosubstituted products were formed, the para-substituted derivative was favored due to steric effects.

In another methodology, the nitration was performed under solvent-free conditions. Under these conditions, the 3-R-2-phenylamino-1,4-naphthoquinone derivatives were

reacted with a mixture (1:1) of oxalic acid and sodium nitrate for several hours at 80 °C. Only the naphthoquinone derivative containing a chlorine atom in position three gave good yields of a mixture containing ortho and para monosubstituted compounds. These results are explained in terms of activating the electron-withdrawing effect of chlorine.

In order to induce nitration with salts, phenylamino-1,4-naphthoquinone derivatives were dissolved in acetic acid and reacted with copper nitrate at room temperature for one hour. Under these experimental conditions, the two mononitrate derivatives were obtained. The preparation of nitrophenyl amino naphthoquinones was also performed using a Michael addition of a nitrated aniline to naphthoquinone in the presence of a Lewis acid, either $CeCl_3$ or $FeCl_3$, in ethanol at room temperature for several hours. Under both catalysts, the monosubstituted derivatives (metha or para) were obtained in good yields. Only the ortho derivative was obtained in rather low yields due to steric hindrance.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions4030026/s1, Figure S1: ^{1}H spectrum to:2-(2-nitrophenylamino)-1,4-naphthoquinone. Figure S2: ^{1}H spectrum to: 2-(3-nitrophenylamino)-1,4-naphthoquinone. Figure S3: ^{1}H spectrum to: 2-(4-nitrophenylamino)-1,4-naphthoquinone. Figure S4: ^{1}H spectrum to: 2-(2,4-dinitrophenylamino)-1,4-naphthoquinone. Figure S5: ^{1}H spectrum to: 2-(2-fluoro-5-nitrophenylamino)-1,4-naphthoquinone. Figure S6: ^{1}H spectrum to: 2-(4-fluoro-3-nitrophenylamino)-1,4-naphthoquinone. Figure S7: ^{1}H spectrum to: 2-(2-fluoro-4-nitrophenylamino)-1,4-naphthoquinone. Figure S8: ^{1}H spectrum to: 3-chloro-2-(4-nitrophenylamino)-1,4-naphthoquinone. Figure S9: 1H spectrum to: 3-chloro-2-(2,4-nitrophenylamino)-1,4-naphthoquinone. Figure S10: 1H spectrum to: 3-bromo-2-(4-nitrophenylamino)-1,4-naphthoquinone. Figure S11: 1H spectrum to: 3-bromo-2-(2,4-nitrophenylamino)-1,4-naphthoquinone.

Author Contributions: Investigation, E.L., S.E.L.-C. and J.A.; Writing—original draft, S.E.L.-C.; Supervision, E.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Acknowledgments: The authors thank CONAHCyT, LOREAL/UNESCO/AMC (G2022).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Da Silva, M.N.; Ferreira, V.F.; De Souza, M.C.B.V. Um Panorama atual da química e da farmacologia de Naftoquinonas, com enfase na ß-Lapachona e derivados. *Quim. Nova* **2003**, *26*, 407–416. [CrossRef]
2. Akiyoshi, T.; Matzno, S.; Sakai, M.; Okamura, N.; Matsuyama, K. The potential of vitamin K_3 as an anticancer agent against breast cancer that acts via the mitochondria-related apoptotic pathway. *Cancer Chemother. Pharmcol.* **2009**, *65*, 143–150. [CrossRef] [PubMed]
3. Chaves-Carballo, K.; Lamoureux, G.V.; Perez, A.L.; Bella, A.; Cechinel, V. Novel one-pot synthesis of a library of 2-aryloxy-1,4-naphthoquinone derivatives. Determination of antifungal and antibacterial activity. *RSC Adv.* **2022**, *29*, 18507–18523.
4. Ahmad, T.; Suzuki, Y.J. Juglone in oxidative stress and cell signaling. *Antioxidants* **2019**, *8*, 91. [CrossRef]
5. Badolato, M.; Carullo, G.; Caroleo, M.C.; Cione, E.; Aiello, F.; Manetti, F. Discovery of 1, 4-naphthoquinones as a new class of antiproliferative agents targeting GPR55. *ACS Med. Chem. Lett.* **2019**, *10*, 402–406. [CrossRef]
6. Liu, Z.; Shen, Z.; Xiang, S.; Sun, Y.; Cui, J.; Jia, J. Evaluation of 1,4-naphthoquinone derivatives as antibacterial agents: Activity and mechanistic studies. *Front. Environ. Sci. Eng.* **2023**, *17*, 31. [CrossRef]
7. Epifano, F.; Genovese, S.; Fiorito, S.; Mathieu, V.; Kiss, R. Lapachol and its congeners as anticancer agents: A review. *Phytoche. Rev.* **2014**, *13*, 37–49. [CrossRef]
8. Majdi, C.; Duvauchelle, V.; Meffre, P.; Benfodda, Z. An overview on the antibacterial properties of juglone, naphthazarin, plumbagin and lawsone derivatives and their metal complexes. *Biomed. Pharmacother.* **2023**, *162*, 114690. [CrossRef]
9. Hsieh, Y.J.; Lin, L.C.; Tsai, T.H. Determination and identification of plumbagin from the roots of *Plumbago zeylanica* L. by liquid chromatography with tandem mass spectrometry. *J. Chromatogr.* **2005**, *1083*, 141–145. [CrossRef]
10. Son, T.G.; Camandola, S.; Arumugam, T.V.; Cutler, R.G.; Telljohann, R.S.; Mughal, M.R.; Moore, T.A.; Luo, W.; Yu, Q.S.; Johnson, D.A.; et al. Plumbagin, a novel Nrf2/ARE activator, protects against cerebral ischemia. *J. Neurochem.* **2010**, *112*, 1316–1326. [CrossRef]
11. Campora, M.; Francesconi, V.; Schenone, S.; Tasso, B.; Tonelli, M. Journey on Naphthoquinone and Anthraquinone Derivatives: New Insights in Alzheimer's Disease. *Pharm. J.* **2021**, *14*, 33. [CrossRef] [PubMed]

12. Nakhate, K.T.; Bharne, A.P.; Verma, V.S.; Aru, D.N.; Kokare, D.M. Plumbagin ameliorates memory dysfunction in streptozotocin induced Alzheimer's disease via activation of Nrf2/ARE pathway and inhibition of β-secretase. *Biomed. Pharmacother.* **2018**, *101*, 379–390. [CrossRef] [PubMed]
13. Ahmad, A.; Syed, F.A.; Singh, S.; Hadi, S.M. Prooxidant activity of resveratrol in the presence of copper ions: Mutagenicity in plasmid DNA. *Toxicol. Lett.* **2005**, *159*, 1–12. [CrossRef] [PubMed]
14. Khan, N.S.; Ahmad, A.; Hadi, S.M. Anti-oxidant, pro-oxidant properties of tannic acid and its binding to DNA. *Chem. Biol. Interact.* **2000**, *125*, 177–189. [CrossRef] [PubMed]
15. Kavaliauskas, P.; Opazo, F.S.; Acevedo, W.; Petraitiene, R.; Grybaitė, B.; Anusevičius, K.; Petraitis, V. Synthesis, biological activity, and molecular modelling studies of naphthoquinone derivatives as promising anticancer candidates targeting COX-2. *Pharm. J.* **2022**, *15*, 541. [CrossRef]
16. Da Silva Júnior, E.N.; de Melo, I.M.; Diogo, E.B.; Costa, V.A.; de Souza Filho, J.D.; Valença, W.O.; Camara, C.A.; de Oliveira, R.N.; de Araujo, A.S.; Emery, F.S.; et al. On the search for potential anti-Trypanosoma cruzi drugs: Synthesis and biological evaluation of 2-hydroxy-3-methylamino and 1,2,3-triazolic naphthoquinoidal compounds obtained by click chemistry reactions. *Eur. J. Med. Chem.* **2012**, *52*, 304–312. [CrossRef]
17. Neves, A.P.; Pereira, M.X.; Peterson, E.J.; Kipping, R.; Vargas, M.D.; Silva-Jr, F.P.; Carneiro, J.W.; Farrell, N.P. Exploring the DNA binding/cleavage, cellular accumulation and topoisomerase inhibition of 2-hydroxy-3-(aminomethyl)-1,4-naphthoquinone Mannich bases and their platinum(II) complexes. *J. Inorg. Biochem.* **2013**, *119*, 54–64. [CrossRef]
18. de Araujo, M.V.; David, C.C.; Neto, J.C.; de Oliveira, L.A.; da Silva, K.C.J.; Dos Santos, J.M.; Alexandre-Moreira, M.S. Evaluation on the leishmanicidal activity of 2-N, N′-dialkylamino-1, 4-naphthoquinone derivatives. *Exp. Parasitol.* **2017**, *176*, 46–51. [CrossRef]
19. Wolstenholm, G.E.W.; O'Conner, C.M. *Quinones in Electron Transport*; Churchill: London, UK, 1961.
20. López López, L.I.; Nery Flores, S.D.; Silva Belmares, S.Y.; Sáenz Galindo, A. Naphthoquinones: Biological properties and synthesis of lawsone and derivatives-a structured review. *Vitae* **2014**, *21*, 248–258. [CrossRef]
21. Valle-Bourroueta, G.; Ugalde-Saldívar, V.M.; Gómez, M.; Ortiz- Frade, L.A.; González, I.; Frontana, C. Magnetic interactions as a stabilizing factor of semiquinone species of lawsone by metal complexation. *Electrochim. Acta* **2010**, *55*, 9042–9050. [CrossRef]
22. Pettit, R.K.; Fakoury, B.R.; Knight, J.C.; Weber, C.A.; Pettit, G.R.; Cage, G.D.; Pon, S.J. Antibacterial activity of the marine sponge constituent cribrostatin. *J. Med. Microbiol.* **2004**, *53*, 61–65. [CrossRef]
23. Verniest, G.; Wang, X.P.; De Kimpe, N.; Padwa, A.J. Heteroaryl cross-coupling as an entry toward the synthesis of lavendamycin analogues: A model study. *Org. Chem.* **2010**, *75*, 424–433. [CrossRef]
24. Bai, X.; Liu, Y.; Wang, H.; Zhang, H. Natural Products from the Marine Sponge Subgenus *Reniera*. *Molecules* **2021**, *26*, 1097. [CrossRef]
25. Kesteleyn, B.; De Kimpe, N. Synthesis of mimosamycin. *J. Org. Chem.* **2000**, *65*, 635–639. [CrossRef]
26. Noriega, S.; Cardoso-Ortiz, J.; López-Luna, A.; Cuevas-Flores, M.D.R.; Flores De La Torre, J.A. The Diverse Biological Activity of Recently Synthesized Nitro Compounds. *Pharm. J.* **2022**, *15*, 717. [CrossRef]
27. Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K.K.; Jonnalagadda, S.B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25*, 1909. [CrossRef] [PubMed]
28. Morawska, K.; Jedlińska, K.; Smarzewska, S.; Metelka, R.; Ciesielski, W.; Guziejewski, D. Analysis and DNA interaction of the profluralin herbicide. *Environ. Chem. Lett.* **2019**, *17*, 1359–1365. [CrossRef]
29. Ribeiro, T.A.; Machado-Ferreira, E.; Guimarães, L.F.; Cavaleiro, J.; Britto, A.M.A.; Redua, N.; Soares, C.A.G. Novel cytotoxic amphiphilic nitro-compounds derived from a synthetic route for paraconic acids. *Colloids Surf. A Physicochem. Eng. Asp.* **2021**, *626*, 126984. [CrossRef]
30. Rice, A.M.; Long, Y.; King, S.B. Nitroaromatic antibiotics as nitrogen oxide sources. *Biomolecules* **2021**, *11*, 267. [CrossRef]
31. Tavera-Hernández, R.; Jiménez-Estrada, M.; Alvarado-Sansininea, J.J.; Nieto-Camacho, A.; López-Muñoz, H.; Sánchez-Sánchez, L.; Escobar, M.L. Synthesis of chrysin, quercetin and naringin nitroderivatives: Antiproliferative, anti-inflammatory and antioxidant activity. *Lett. Drug Des. Discov.* **2021**, *18*, 795–805. [CrossRef]
32. Toro, P.M.; Acuña, A.; Mallea, M.; Lapier, M.; Moncada-Basualto, M.; Cisterna, J.; Brito, I.; Klahn, H. Condensation and Substitution Products Obtained in Reactions of Isomeric Bromo-Nitrofuraldehydes with Ferrocenylamine: Electrochemistry and Anti-Parasitic Evaluation. *J. Organomet. Chem.* **2019**, *901*, 120946. [CrossRef]
33. Adedapo, A.D.; Ajayi, A.M.; Ekwunife, N.L.; Falayi, O.O.; Oyagbemi, A.; Omobowale, T.O.; Adedapo, A.A. Antihypertensive effect of Phragmanthera incana (Schum) Balle on NG-nitro-L-Arginine methyl ester (L-NAME) induced hypertensive rats. *J. Ethnopharmacol.* **2020**, *257*, 112888. [CrossRef] [PubMed]
34. Ghatge, S.; Yang, Y.; Moon, S.; Song, W.Y.; Kim, T.Y.; Liu, K.H.; Hur, H.G. A novel pathway for initial biotransformation of dinitroaniline herbicide butralin from a newly isolated bacterium *Sphingopyxis* sp. strain HMH. *J. Hazard. Mater.* **2021**, *402*, 123510. [CrossRef] [PubMed]
35. Calandra, J.C.; Adams, E.C., Jr. The preparation of amine derivatives of 2-chloro-1, 4-naphthoquinone. *J. Ame. Chem. Soc.* **1950**, *72*, 4804. [CrossRef]
36. Queiroz, J.F.D.; Carneiro, J.W.D.M.; Sabino, A.A.; Sparrapan, R.; Eberlin, M.N.; Esteves, P.M. Electrophilic aromatic nitration: Understanding its mechanism and substituent effects. *J. Org. Chem.* **2006**, *71*, 6192–6203. [CrossRef]
37. Capobianco, A.; Landi, A.; Peluso, A. Is Aromatic Nitration Spin Density Driven? *Chemistry* **2021**, *3*, 1286–1301. [CrossRef]

38. Liljenberg, M.; Stenlid, J.H.; Brinck, T. Mechanism and regioselectivity of electrophilic aromatic nitration in solution: The validity of the transition state approach. *J. Mol. Model.* **2018**, *24*, 1–3. [CrossRef]
39. Pratt, Y.T. Quinolinequinones. VI. Reactions with aromatic amines1. *J. Org. Chem.* **1962**, *27*, 3905–3910. [CrossRef]
40. Gigante, B.; Prazeres, A.O.; Marcelo-Curto, M.J. Mild and selective nitration by "Claycop". *J. Org. Chem.* **1994**, *60*, 3445–3447. [CrossRef]
41. Leyva, E.; Baines, K.M.; Espinosa-González, C.G.; Magaldi-Lara, D.A.; Loredo-Carrillo, S.E.; De Luna-Méndez, T.A.; López, L.I. 2-(Fluoro-) and 2-(methoxyanilino)-1, 4-naphthoquinones. Synthesis and mechanism and effect of fluorine substitution on redox reactivity and NMR. *J. Fluor. Chem.* **2015**, *180*, 152–160. [CrossRef]
42. Patel, S.S.; Patel, D.B.; Patel, H.D. Synthetic protocols for aromatic nitration: A review. *ChemistrySelect* **2021**, *6*, 1337–1356. [CrossRef]
43. Urben, P. *Bretherick's Handbook of Reactive Chemical Hazards*; Elsevier: Amsterdam, The Netherlands, 2017.
44. Millen, D.J. 509. Vibrational spectra of ionic forms of oxides and oxy-acids of nitrogen. Part IV. Raman spectral evidence of ionisation in crystalline nitronium salts. The constitution of solid dinitrogen pentoxide. Note on the spectrum of the perchlorate ion. *J. Chem. Soc. (Resumed.)* **1950**, 2606–2612. [CrossRef]
45. Win, T.; Yerushalmi, S.; Bittner, S. Direct nitration of 3-arylamino-2-chloro-1,4-naphthoquinones. *Synthesis* **2005**, *10*, 1631–1634. [CrossRef]
46. Kim, E.K.; Bockman, T.M.; Kochi, J.K. Electron-transfer mechanism for aromatic nitration via the photoactivation of EDA (electron donor-acceptor) complexes. Direct relationship to electrophilic aromatic substitution. *J. Am. Chem. Soc.* **1993**, *115*, 3091–3104. [CrossRef]
47. Leyva, E.; Baines, K.M.; Espinosa-González, C.G.; López, L.I.; Magaldi-Lara, D.A.; Leyva, S. Synthesis of novel 2-(fluoroanilino)-3-(2, 4-dinitroanilino) derivatives of 1, 4-naphthoquinone. *Tetrahedron Lett.* **2015**, *56*, 5248–5251. [CrossRef]
48. Baghernejad, B.; Heravi, M.M.; Oskooie, H.A.; Be-heshtiha, Y.S. Synthesis and biological evaluation of some chrysene derivatives an efficient and regioselective nitration of phenols using NH4NO3, KHSO4. *Gazi Univ. J. Sci.* **2009**, *3*, 169–173.
49. Olah, G.A.; Kunh, S.J.; Flood, H.; Evans, J.C. Aromatic substitution. XIII. 1a comparison of nitric acid and mixed acid nitration of alkylbenzenes and benzene with nitronium salt nitrations. *J. Am. Chem. Soc.* **1962**, *84*, 3687–3693. [CrossRef]
50. Fisher, J.W. The chemistry of dinitrogen pentoxide in nitro compounds: Recent advances in synthesis and chemistry. In *Advances in Chemistry Series*; Feuer, H., Arnold, A.T., Eds.; VCH Publishers, Inc.: New York, NY, USA, 1990.
51. Loupy, A. Solvent-free reactions. In *Modern Solvents in Organic Synthesis*; Springer: Berlin/Heidelberg, Germany, 1999; pp. 153–207.
52. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. New solvent-free organic synthesis using focused microwaves. *Synthesis* **1998**, *9*, 1213–1234. [CrossRef]
53. Beheshti, S.; Kianmehr, E.; Yahyaee, M.; Tabatabai, K. Facile and efficient selective mono-nitration of phenols under solvent-free conditions. *Bull. Korean Chem. Soc.* **2006**, *27*, 1056–1058. [CrossRef]
54. Lampman, G.M.; Pavia, D.L.; Kriz, G.S. *Introduction to Spectroscopy*, 4th ed.; Wiley-Intrescience Publication: Hoboken, NJ, USA, 2010.
55. Lisboa, C.S.; Santos, G.V.; Vaz, G.B.; De Lucas, N.C.; Eberlin, N.M.; Garden, J.S. C-H Functionalization of 1,4-naphthoquinone by oxidative coupling with anilines in the presence of a catalytic quantity of copper(II) acetate. *J. Org. Chem.* **2011**, *76*, 5264–5273. [CrossRef]
56. Leyva, E.; López, L.I.; Loredo-Carrillo, S.E.; Rodríguez-Kessler, M.; Montes-Rojas, A. Synthesis, spectral and electrochemical characterization of novel 2-(fluoroanilino)-1, 4-naphthoquinones. *J. Fluor. Chem.* **2011**, *132*, 94–101. [CrossRef]
57. Leyva, E.; Loredo-Carrillo, S.E.; López, L.I. Catalytic, ultrasonic, and microwave-assisted synthesis of naphthoquinone derivatives by intermolecular and intramolecular N-arylation reactions. In *Green Sustainable Process for Chemical and Environmental Engineering and Science*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 231–264.