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The addition of hydrogen chloride and hydrogen bromide to phenyliminoquinone and its *N*-oxide

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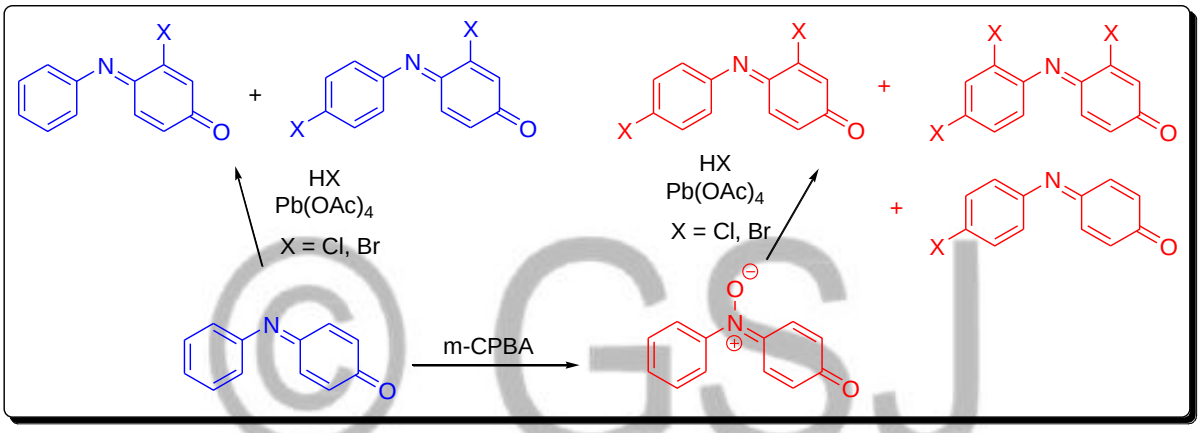
Abstract



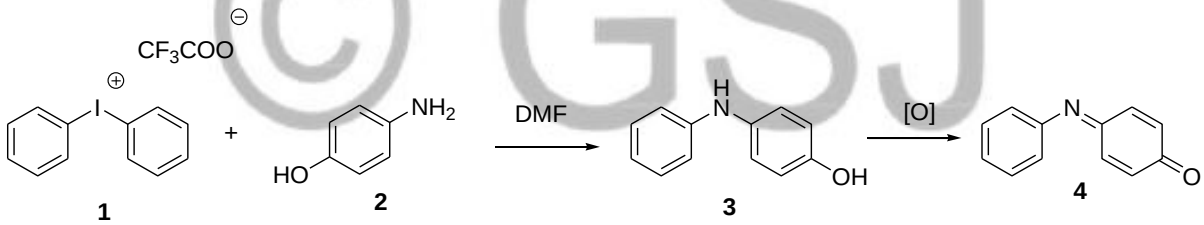
The carbon-halogen bond can be used as a precursor in forming a range of bonds such as carbon-carbon, carbon-nitrogen, and carbon-oxygen bonds. This is of great interest in the development of the reactions of azaquinone as it will allow subsequent elaboration of the structure to access useful motifs as part of drug development. The addition of hydrogen chloride and hydrogen bromide to 4-(phenylimino)cyclohexa-2,5-dien-1-one, and its *N*-oxide, 4-oxo-*N*-phenylcyclohexa-2,5-dien-1-imine oxide, are reported. The halogenation of azaquinone gave substitution products of the quinoid ring. However, the investigation of the halogenation of the *N*-oxide gave direct substitution of the phenyl ring, changing the selectivity of the reaction and giving the possibility of controlling the product distribution. The concurrent loss of the *N*-oxide functionality in the products from the halogenation reactions suggests that the mechanism of halogenation of the phenyl group in the *N*-oxide is from nucleophilic addition rather than the radical reaction observed with azaquinone. These halogenated compounds can now serve as a building block to access new bioactive scaffolds.

Keywords: iminoquinone, bromination, chlorination, resorcinol, *N*-oxide, regiochemistry

Introduction

There is an ongoing need for new and improved therapeutics, with extensive progress made in the development of anti-cancer treatments and the search for novel antimicrobials.[1] However, disease modifying therapies remain extremely scarce for neurodegenerative diseases which is of particular concern with an aging global population.

One notable aspect of this challenge is the limited numbers of fragments present in FDA-approved drugs and experimental drugs[2] and as a result, not only do these molecules only occupy a fraction of the possible chemical space,[3] it increases the propensity for detrimental off-target activity. This situation provides an opportunity to organic chemists to identify new bioactive scaffolds, novel strategies for the controlled incorporation of critical functionality and thereby discover and utilise selective modes of action.



Scheme 1: *N*-Arylation of 4-hydroxyaniline with diaryliodonium trifluoroacetate

During our studies on the arylation of anilines using diaryliodonium salts, we identified that the difference in reactivity between nucleophilic groups could be exploited in the use of polyfunctional substrates, for example in the selective formation of diarylamines.[4] Arylation reactions of diaryliodonium salts with species containing multiple nucleophilic sites may show selectivity, as in the case of hydroxyanilines and the resulting products can undergo further transformations, extending the utility still further. In the analysis of the reaction of 4-hydroxyaniline, **2** we identified azaquinone, **4** as a minor by-product which, given the extensive biology and chemistry of quinones, prompted us to consider whether this structural motif had potential as a new molecular scaffold (Scheme 1).

Azaquinones constitute a core structure in several important natural products (Fig. 1),[5,6] some of which are key abiotic and biological compounds, which intercalate with DNA.[7] Azaquinones therefore represent a new frontier for the design and generation of molecular complexity.[8]

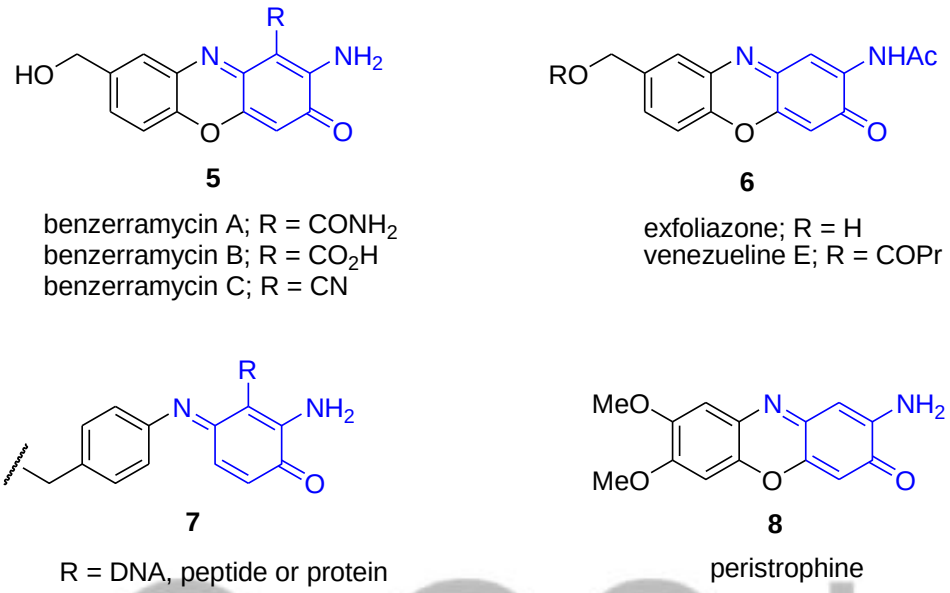


Fig. 1: Known bioactive azaquinones

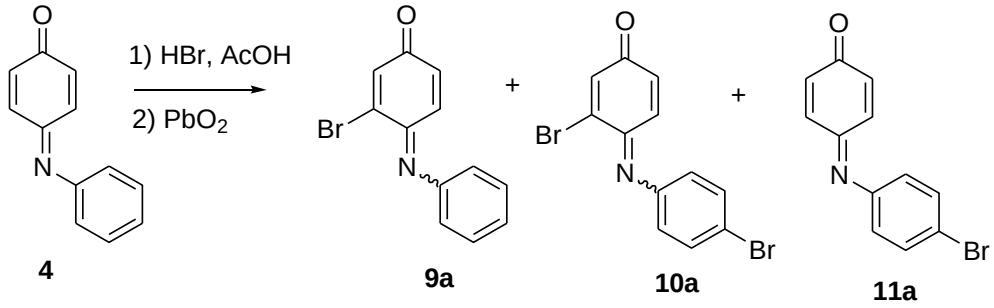
The introduction of halogens into the azaquinone ring opens a gateway to further chemical reactions through the reactivity of the carbon-halogen bond e.g. via modern cross-coupling reactions such as the Suzuki-Miyaura and Mizoroki-Heck reactions.[9,10]

In addition, the potential of subsequent desymmetrisation afforded by the terminal nitrogen substituent gives a further element of complexity over the equivalent quinone framework.

Results and Discussion

Initial studies on the reaction of hydrobromic acid with azaquinone, **4** have been reported by Burmistrov et al.[11] It was reported that the nucleophilic addition of bromide was to the α,β-unsaturated ketone, however the position relative to the *N*-Ar substituent was not discussed. Aqueous hydrobromic acid was added to azaquinone in acetic acid at room temperature, and organic extracts from the reaction mixture were treated with lead (IV) oxide (Scheme 2) to convert the phenol intermediate to the azaquinone system.

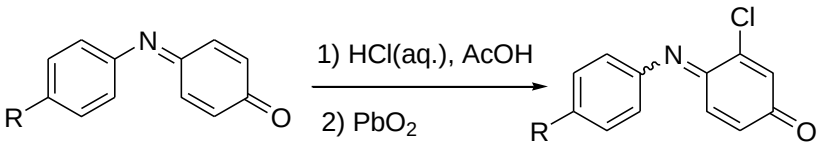
From the reaction, compounds **9a**, **10a**, and **11a** were isolated in 36%, 32%, and 3% respectively although ^{1}H NMR data was provided only for **10a**.[11] Compound **9a** was characterised using melting point and elemental analysis only while melting point data was given for **11a**. This level of characterisation is surprising given the amount of compound **9a** that was isolated (94 mg). These are insufficient data to correctly assign the regiochemistry of any substitution and thus the identity of these compounds. It was therefore needful to consider this reaction process in detail.



Scheme 2: Addition of hydrobromic acid to azaquinone

The reported reactions were repeated by ourselves by adding aqueous hydrobromic acid to azaquinone in acetic acid and stirring at room temperature for 30 min. Preliminary studies were done using lead (IV) oxide, however lead (IV) acetate was also considered as an alternative for the oxidation step as it is a more selective oxidising agent.[12] However, the results were similar, therefore, lead (IV) acetate was used for the remaining studies because it resulted in less by-products evident by TLC. The combined organic products were oxidised, and compounds **9a** and **10a** were isolated by two-stage column chromatography (SiO_2 1:4 ethylacetate-petrol followed by RP (C18) 1:1 MeCN-H_2O) from the crude reaction mixture (32% and 36% respectively).

The addition of hydrochloric acid to azaquinone was also reported by Burmistrov et al.[13] The regioselectivity of nucleophilic addition to *N*-phenylquinoneimine is determined by electrophilicity of the substrate, nucleophilicity of the reagent, and hardness of the latter.[14] Hard nucleophiles ($Cl^{\ominus}$, $Br^{\ominus}$) add to *N*-phenylquinoneimine in protic media at the ortho position to the nitrogen atom i.e. to the α,β unsaturated ketone (Scheme 3).[15]

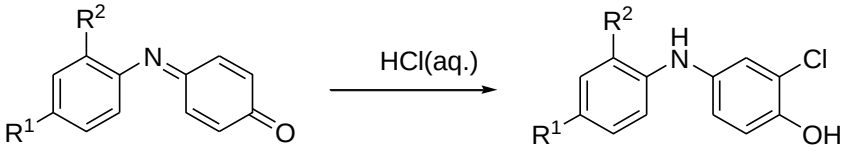


4, 12a,b **9b, 13a,b**

R = H **(4)**, R = OMe **(12a),** R = I **(12b)**

Scheme 3: Reaction of hydrochloric acid with azaquinones

However, when strong electron-withdrawing substituents are introduced into the *N*-aryl fragment, the electrophilicity of the quinoneimine is increased and products from addition to the α,β unsaturated imine are formed (Scheme 4).[13,16]



14a,b **15a,b**

R^1 = H, R^2 = NO_2 **(a)**, R^1 = NO_2, R^2 = H **(b)**

Scheme 4: Influence of electron-withdrawing groups on the chlorination of azaquinones

To investigate the halogenation reactions of azaquinone and its *N*-oxide, an independent synthesis was carried out to access sufficient amounts of azaquinone due to the low yield obtained in the *N*-arylation reaction.[4(b)]

Azaquinone was prepared by the oxidation of 4-hydroxydiphenylamine with Fetizon's reagent,[17] giving excellent yield.

The ^{1}H NMR spectrum of azaquinone (Fig. 2) shows the four quinoid protons are different, having peaks as doublet of doublets, which demonstrates the potential different reactivity towards nucleophiles of the different positions.

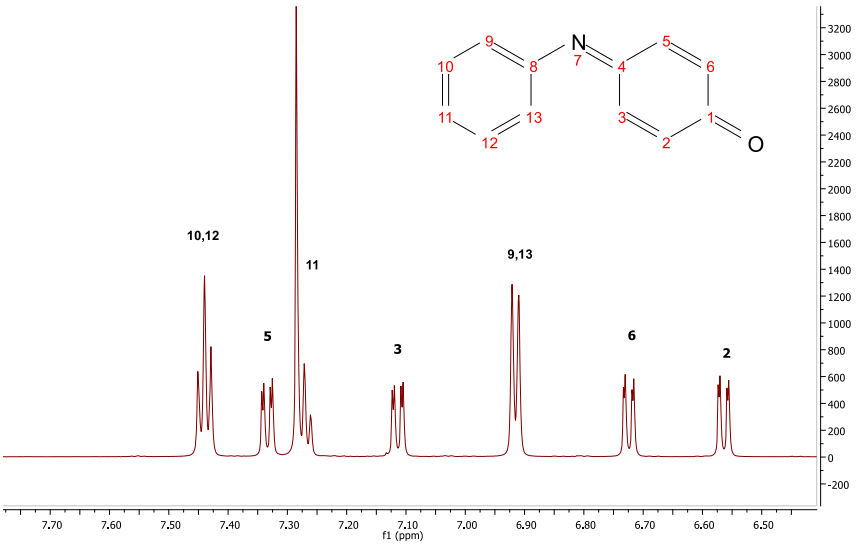
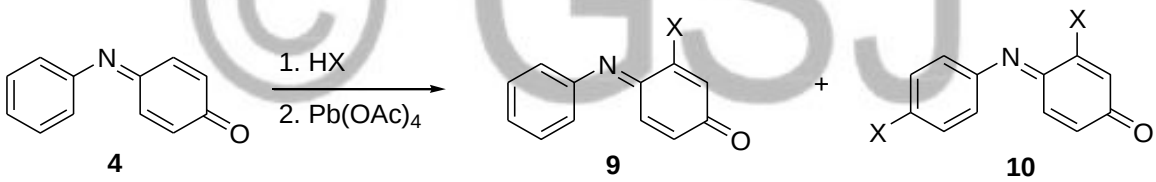


Figure 2: ^{1}H NMR spectrum of azaquinone

Although the literature report[18] gives the ^{1}H NMR data of azaquinone as doublet of doublets, the chemical shifts were not assigned to their respective protons. This we have done with the aid of modern analytical methods (2D NMR and X-ray) and therefore confirmed the regiochemistry.

Table 1: Halogenation of azaquinone **4**



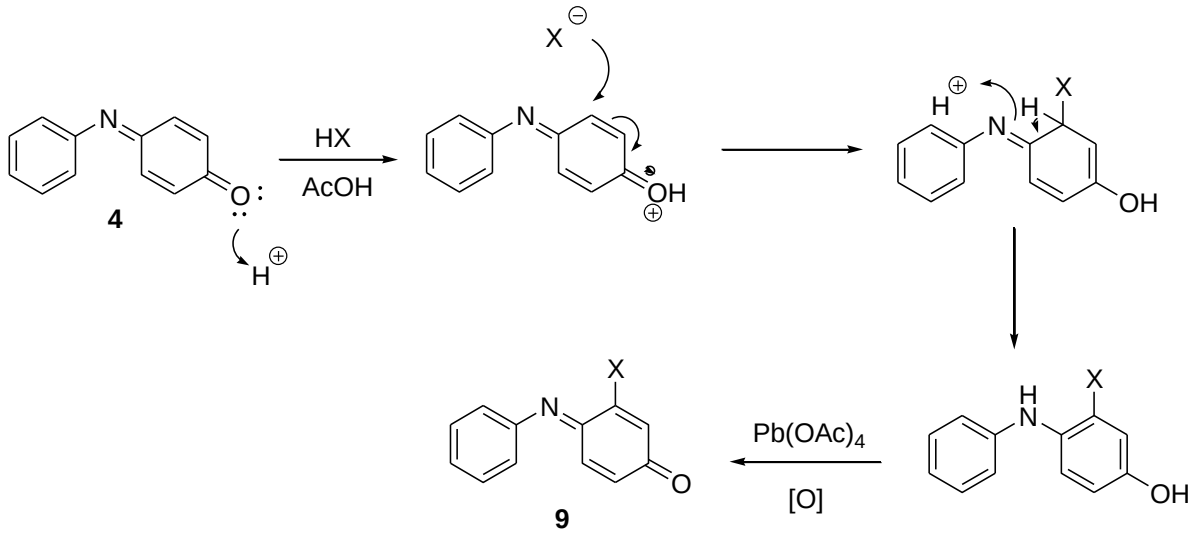
X = Br **(a)**, Cl **(b)**

Entry	**HBr/ HCl**	**Monohalo (quinoid ring) Yield %**	**Dihalo Yield %**
1	HBr	32 **(9a)**	36 **(10a)**
2	HBr[a]	60 **(9a)**	nd
3	HCl	60 **(9b)**	nd
4	HCl[a]	60 **(9b)**	nd

[a] with resorcinol 100 mol%, 'nd' not detected

The halogenation reactions were carried out by adding aqueous hydrobromic acid/concentrated hydrochloric acid to azaquinone **4** in acetic acid with and without

resorcinol, and organic extracts from the reaction mixture were treated with lead (IV) acetate giving the substituted products in average yields as shown in Table 1.



Scheme 5: Mechanism for the halogenation of azaquinone

The bromination of azaquinone **4** gives both mono-substituted (quinoid ring) **9a** and di-substituted (phenyl and quinoid rings) **9a** products. The reactions of hydrobromic or hydrochloric acid with azaquinone occurs by addition to the α,β-unsaturated ketone to give the 4-hydroxydiphenylamine which is then oxidised to give the haloazaquinone **9** (Scheme 5). Bromination of the phenyl ring at the para position was found to occur as a competing process in the addition of HBr to azaquinone, giving the di-substituted compound **10a**. The addition of resorcinol or other radical scavengers to the reaction mixture changes the composition of the reaction mixture and eliminates the bromination of the phenyl ring, giving **9a** only.

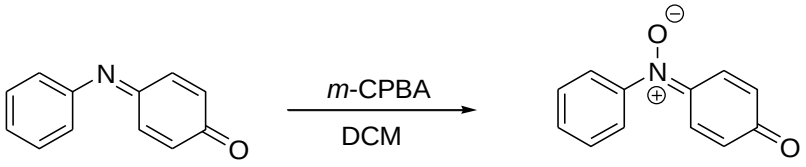
In a similar way to the bromination reactions, the synthesized compounds reported in the literature[13] from the chlorination of azaquinone were analysed by their melting points, infrared spectroscopy and elemental analyses. These data could not have unambiguously assigned the position of the chlorine atom, hence the regiochemistry of these compounds remains to be confirmed.

The chlorination of azaquinone, however, is more selective and gives only the mono-substituted (quinoid ring) product **9b**. It should be noted that the chlorination of the phenyl ring as a competing process was not observed in the treatment of azaquinone with HCl, therefore the product of the reaction with resorcinol was found to be the

same as when resorcinol was not added to the reaction mixture indicating the lower reactivity of the chlorination reagent for aromatic rings.

Based on the literature report of azaquinone-*N*-oxide[19,20] and the effect of electron withdrawing groups on the halogenation of azaquinone (Scheme 4), it was of interest to see if the *N*-oxide **16** could serve as a directing and/or protecting group with the halogenation reactions.

Azaquinone *N*-oxide was prepared from the oxidation of azaquinone using meta-chloroperoxybenzoic acid (*m*-CPBA) in DCM at room temperature for 24 h (Scheme 6).[19]



4 **16**

Scheme 6: Preparation of azaquinone-*N*-oxide from azaquinone

The structure of the *N*-oxide was confirmed by NMR and by the determination of the crystal structure (Figure 3).

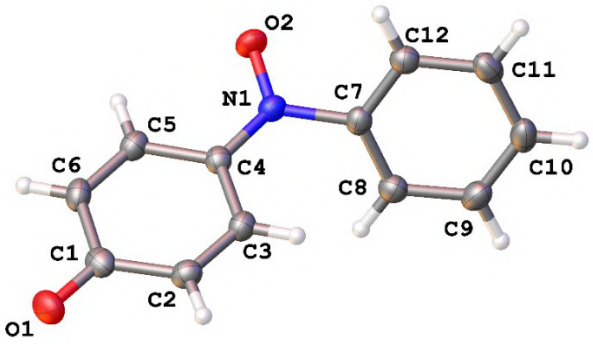
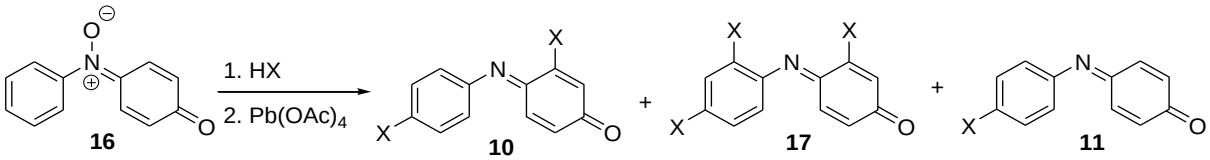


Figure 3: Crystal structure of azaquinone-*N*-oxide **16**

As the halogenation of the *N*-oxide is an unexplored reaction, the same method that was used for the halogenation of azaquinone was employed.

Table 2: Halogenation of azaquinone-*N*-oxide **16**

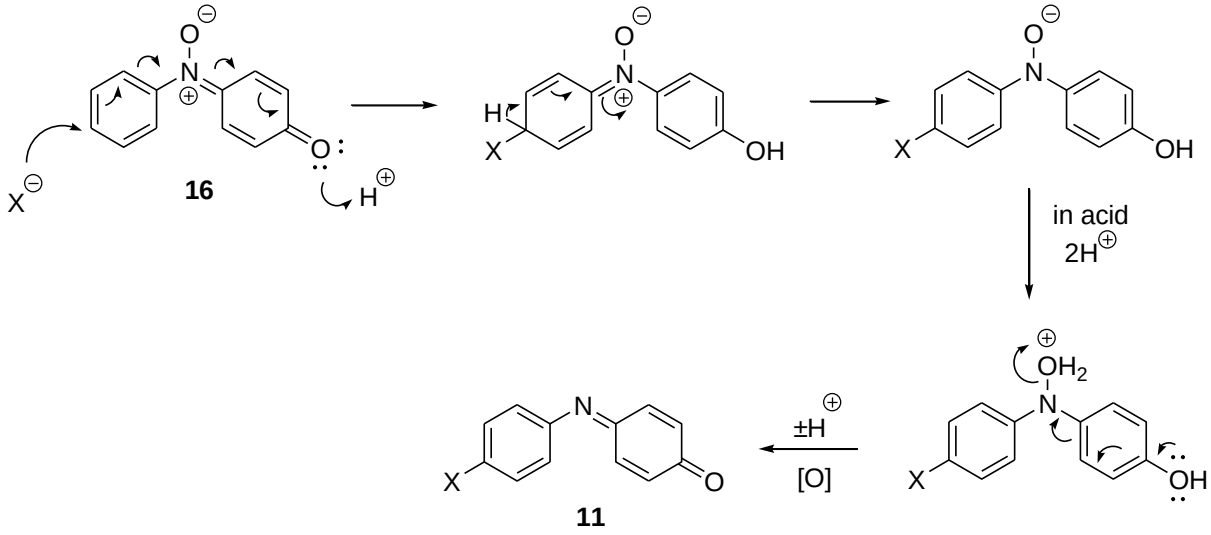


X = Br **(a)**, Cl **(b)**

Entry	HBr/ HCl	Trihalo Yield	Dihalo Yield	Monohalo (quinoid ring) Yield	Monohalo (phenyl ring) Yield
1	HBr	30% **(17a)**	37% **(10a)**	nd	7% **(11a)**
2	HBr[a]	nd	47% **(10a)**	26% **(9a)**	nd
3	HCl	nd	70% **(10b)**	nd	12% **(11b)**
4	HCl[a]	nd	42% **(10b)**	25% **(9b)**	nd

[a] with resorcinol 100 mol%, 'nd' not detected

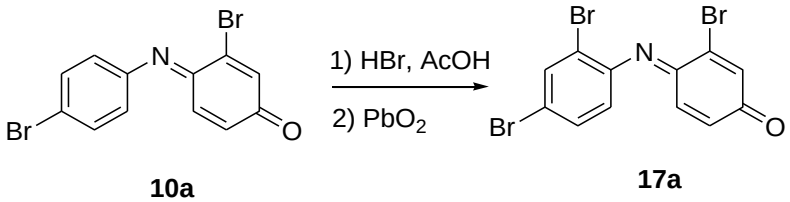
The bromination of azaquinone-*N*-oxide **16** gave the tri-substituted product **17a**, the di-substituted product **10a**, and the mono-substituted product (phenyl ring) **11a** (Table 2). It should be noted that no *N*-oxides, including **16** were recovered. The addition of resorcinol to the bromination of the *N*-oxide however changed the composition of the reaction mixture. Compounds **11a** and **17a** were not observed but the di-substituted product **10a** was still observed with the mono-substituted (quinoid-ring) product **9a** being formed. The observance of **10a** suggests that the bromination of the phenyl ring is not eliminated in the bromination of the *N*-oxide using resorcinol and therefore is probably not a radical bromination process but a nucleophilic addition.



Scheme 7: Mechanism for the halogenation of azaquinone-*N*-oxide

Compound **10a** is a common product from the bromination reactions of both the azaquinone **4** and the *N*-oxide **16.** The tri-substituted product **17** and the mono-substituted (phenyl ring) product **11a**, however, were observed in the direct bromination of the *N*-oxide but not in the bromination of azaquinone. This suggests that the phenyl ring in the *N*-oxide is less electron rich than in the azaquinone, and so more electrophilic than the azaquinone. The loss of the *N*-oxide in the products from the bromination reactions suggests that the mechanism of bromination of the phenyl group is nucleophilic addition rather than the radical reaction which is observed in the azaquinone bromination reactions.

The mono-substituted product (phenyl ring), compound **11a**, is also one of the products formed in the bromination of the *N*-oxide, showing that the *N*-oxide results in direct halogenation to the phenyl ring suggesting the order of reaction as no mono-substituted (phenyl ring) product was observed with the azaquinone i.e. bromination of the phenyl ring first and then bromination of the azaquinone group as described when the azaquinone itself was the substrate.



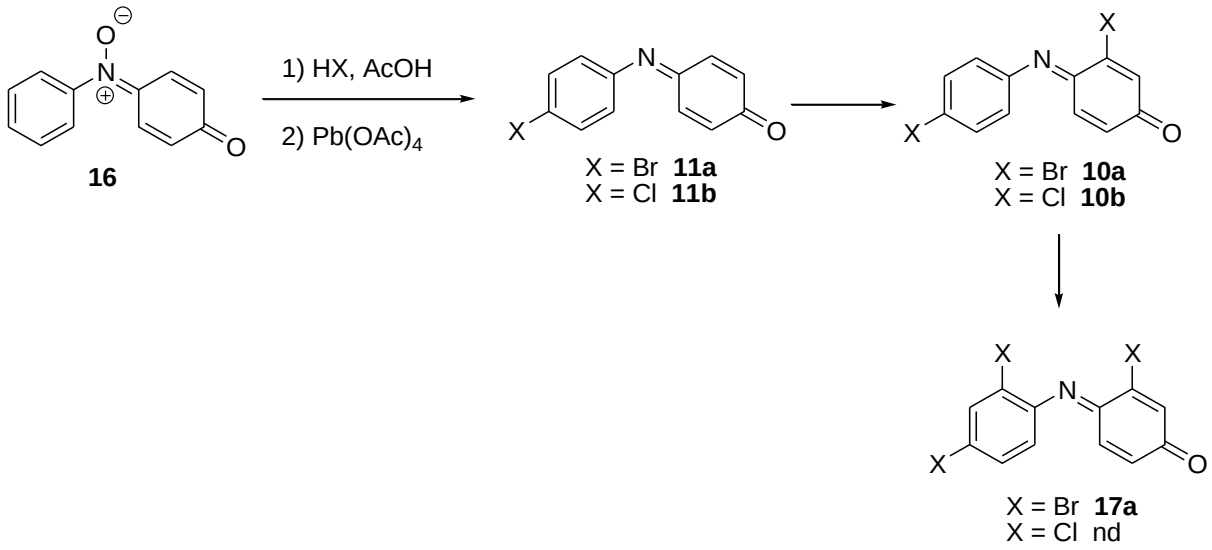
Scheme 8: Addition of hydrobromic acid to di-substituted azaquinone

It had been earlier reported[11] that compound **17a** can be formed by further brominating compound **10a** in the absence of resorcinol (Scheme 8) but it has been observed in this work as one of the products in the direct bromination of the *N*-oxide. The observation that compound **17a** can only be made from azaquinone under more forcing conditions supports the suggestion that the *N*-oxide is brominated before its loss of oxygen and conversion to azaquinone.

The chlorination of the *N*-oxide, however, gives the di-substituted product **10b** and the mono-substituted (phenyl ring) product **11b**. As observed in the bromination of the *N*-oxide, there appears to be a different selectivity in this reaction from the chlorination of azaquinone. Whilst the chlorination of azaquinone gives the mono-substituted (quinoid ring) product **9b**, the chlorination of its *N*-oxide gives the di-substituted product **10b** and the mono-substituted (phenyl ring) product **11b,** which indicates the preference of the *N*-oxide for the reaction of the phenyl ring and that this occurs first. This can be explained from the fact that the *N*-oxide is a more electrophilic substrate than the azaquinone like the bromination result, therefore making the *N*-oxide more reactive to nucleophiles. This selectivity and the non-observance of *N*-oxide products, which was also the case in the bromination of the *N*-oxide, suggests that the loss of oxygen occurs during or after the halogenation (Scheme 7).

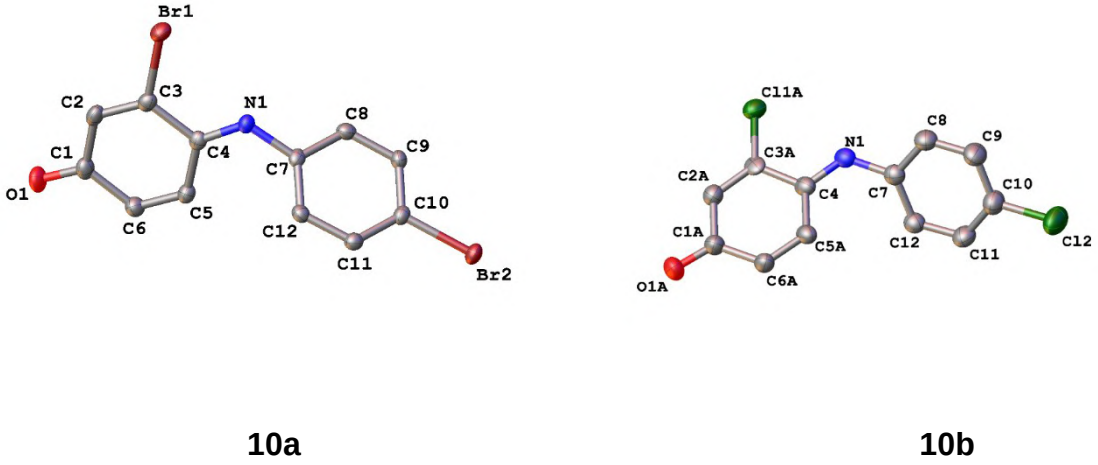
The reaction of azaquinone *N*-oxide with hydrochloric acid was also carried out with the addition of resorcinol. The di-substituted product **10b** is observed together with the mono-substituted (quinoid ring) product **9b.** This observation is similar to that seen with the addition of resorcinol to the bromination of the *N*-oxide. Two possible substitution products – di-substituted product and mono-substituted product (quinoid ring) are formed when resorcinol is added to the halogenation of azaquinone *N*-oxide.

The order of reaction for the halogenation of azaquinone-*N*-oxide should therefore be as shown in Scheme 9.



Scheme 9: General mechanism for the halogenation of azaquinone-*N*-oxide **16**

The regiochemistry of the compounds were determined using COSY and NOESY spectra (see Supporting information) with the position of halogen attachment on the quinoid ring confirmed by determination of the crystal structures (Fig. 4).

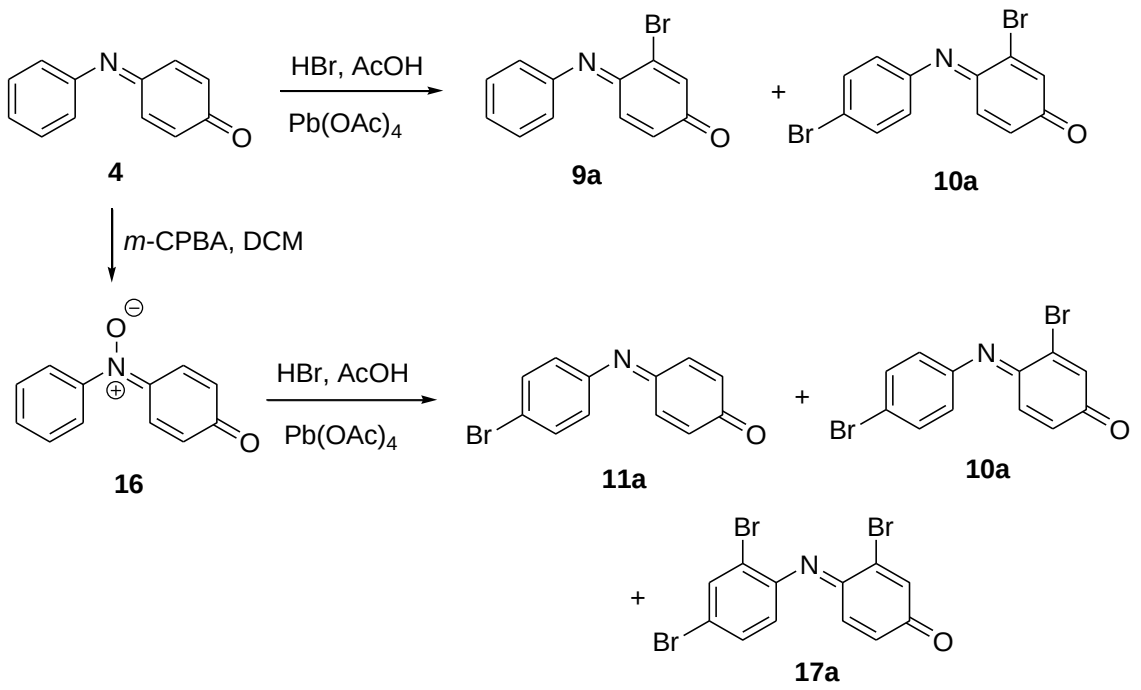


10a **10b**

Figure 4: Crystal structures of **10a** and **10b**

Conclusion

The halogenation of azaquinone is selective allowing targeted functionalisation while azaquinone *N*-oxide gives direct halogenation to the phenyl ring, changing the selectivity of the reaction (Scheme 10). The mechanism of the halogenation of azaquinone and its *N*-oxide have been established with/without the addition of resorcinol.



Scheme 10: Bromination of azaquinone and azaquinone-*N*-oxide

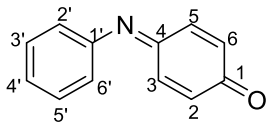
The reactivity of the carbon-halogen bond makes these synthesised halo azaquinones good substrates for cross-coupling reactions.

Experimental Section

Materials and Methods

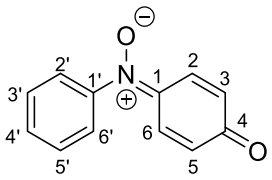
Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a positive pressure of nitrogen. Anhydrous solvents were prepared in accordance with standard protocols. Mettler PB 303-L analytical balance was used to weigh all reagents. Infrared spectra were recorded on a Nicolet Avatar 370DTGS FT-IR spectrometer with internal calibration. ^{1}H, ^{13}C, COSY, NOESY and HSQC NMR spectra were recorded on a Bruker 300 MHz and 700 MHz spectrometers with residual protic solvent as an internal reference. Elemental analyses were carried out at London Metropolitan University and are reported as the average of two runs. Mass Spectra and accurate masses were recorded using the SAgE Mass Spectrometry Facility (Newcastle University). Melting points were recorded on a Gallenkamp MF-370 melting point apparatus and are uncorrected.

4-(Phenylimino)cyclohexa-2,5-dien-1-one, 4



To a solution of 4-hydroxydiphenylamine (3.7 g, 20 mmol) in toluene (800 mL) was added Ag_2CO_3/Celite (12.0 g, 21.1 mmol) in one portion. The resulting mixture was vigorously stirred for 24 h at RT. The reaction mixture was then filtered through a 1 cm thick pad of Celite, washing with toluene (100 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by chromatography (SiO_2 1:4 ether-petrol) gave azaquinone **4** as an orange solid (2.81 g, 15.4 mmol, 77%). R_f = 0.37 (SiO_2 1:4 ether-petrol); Mp 98–100 °C from DCM (lit.,[16] 101–102 °C from toluene); IR (neat) 1643, 1319, 1168, 873, 794, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (2H, t, *J* 8.8 Hz, H3', H5'), 7.24 (1H, dd, *J* 10.0, 2.7 Hz, H5), 7.18 (1H, t, *J* 8.0 Hz, H4'), 7.02 (1H, dd, *J* 10.3, 2.6 Hz, H3), 6.82 (2H, d, *J* 7.6 Hz, H2', H6'), 6.63 (1H, dd, *J* 10.1, 2.2 Hz, H6), 6.47 (1H, dd, *J* 10.3, 2.2 Hz, H2); ^{13}C NMR ($CDCl_3$) δ 187.7 (C1), 157.4 (C4), 149.4 (C1') 141.9 (C5), 133.5 (C2), 132.9 (C6), 129.1(C3', C5'), 128.3 (C3), 126.2 (C4'), 120.6 (C2', C6'); *m/z* (ESI) 185 (M+2, 15%), 184 ($M+H^+$, 100). Found: $M+H^+$, 184.1019. $C_{12}H_{10}NO$ requires 184.0762. Anal Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.76; H, 4.74; N, 7.57.

4-Oxo-*N*-phenylcyclohexa-2,5-dien-1-imine oxide, 16



m-CPBA (0.94 g, 5.46 mmol) was added in small portions to a solution of azaquinone (0.5 g, 2.73 mmol) in dichloromethane (100 mL) over a 5 min period and stirred for 24 h at RT. The solvent was removed in vacuo to give the crude product which was recrystallized with ether-petrol to give **16** as a yellow solid (0.40 g, 2.0 mmol, 74%); R_f = 0.27 (SiO_2 1:4 ethylacetate-petrol + 1% v/v triethylamine); Mp 136–138 °C (ether-petrol), lit.,[17] 141–142 °C(petrol-benzene); IR υ_{max}/cm^{-1} (neat) 3048, 1617, 1592, 1488, 1465, 1438, 1377; ^1H NMR 700MHz ($CDCl_3$) δ 8.06 (1H, dd, *J* 10.2, 2.9 Hz, H2), 7.61 (1H, ddt, *J* 8.6, 7.4, 1.2 Hz, H4'), 7.57 (2H, t, *J* 8.6 Hz, H3', H5'), 7.49 (2H, d, *J* 8.6 Hz, H2', H6'), 7.20 (1H, dd, *J* 10.2, 2.9 Hz, H6), 6.68 (1H, dd, *J* 10.2, 2.0 Hz, H3), 6.27

(1H, dd, *J* 10.2, 2.0 Hz, H5); ^{13}C NMR ($CDCl_3$) δ 186.4 (C4), 171.2 (C1), 145.5 (C1'), 143.5 (C3', C5'), 132.0 (C3), 131.4 (C4'), 129.6 (C6), 128.5(C2), 126.5 (C5), 124.5 (C2', C6'); *m/z* (ESI) 201 (15%), 200 ($M+H^+$, 100). Found: $M+H^+$, 200.0823. $C_{12}H_{10}NO_2$ requires 200.0712. Anal Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.24; H, 4.42; N, 6.91.

Typical procedure for the addition of HBr to azaquinone, **4** or azaquinone *N*-oxide, **16**

48% aqueous hydrobromic acid (8.8 mmol, 1 mL) was added dropwise to a solution of azaquinone, **4** (1.0 g, 5.46 mmol) or azaquinone-*N*-oxide, **16** (1.0 g, 5.0 mmol) in acetic acid (75 mL). The solution was stirred at RT for 30 min and its colour changed from orange to blue. The reaction mixture was diluted with water (200 mL) and extracted with DCM (3 × 150 mL). The organic extracts were washed with water (3 × 100 mL), dried over sodium sulfate and stirred with lead (IV) acetate (8.0 g, 18 mmol) at RT for 1 h. The reaction mixture was then filtered to remove the oxidising agent and the solvent removed in vacuo to give the crude product.

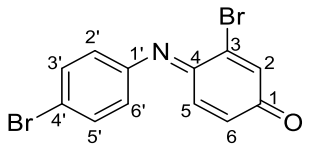
Azaquinone **4** reaction with HBr

Purification by chromatography (SiO_2 1:4 ethylacetate-petrol) and further purification by RP C18 (1:1 MeCN-H_2O) gave **9a** and **10a** as the two major products.

Azaquinone *N*-oxide **16** with HBr

Purification by chromatography (SiO_2 1:4 ethylacetate-petrol) and further purification by RP (C18) (7:3 MeCN-H_2O) gave three products **9a**, **11a** and **17a**. Bromination reaction with resorcinol gave **9a** and **10a**.

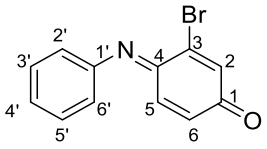
(*E*)-3-Bromo-4-((4-bromophenyl)imino)cyclohexa-2,5-dien-1-one, 10a



An orange solid, (0.67 g, 1.96 mmol, 36%), R_f = 0.86 (SiO_2 1:4 ethylacetate-petrol); Mp 100–102 °C (THF), lit.,[13] 113-114 °C; IR υ_{max}/cm^{-1} (neat) 3059, 2952, 1773, 1661, 1636, 1573, 1560, 1473, 1399, 1380, 1326; ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.45 (2H, d, *J* 8.6 Hz, H3', H5'), 7.14 (1H, d, *J* 2.1 Hz, H2), 7.00 (1H, d, *J* 10.2 Hz, H5), 6.69 (2H,

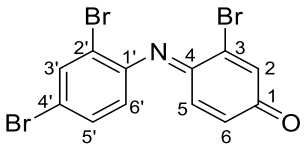
d, *J* 8.6 Hz, H2', H6'), 6.46 (1H, dd, *J* 10.2, 2.1 Hz, H6); ^{13}C NMR ($CDCl_3$) δ 185.0 (C1), 153.5 (C4), 147.7 (C1'), 140.2 (C3), 136.2 (C2), 132.7 (C6), 132.3 (C3', C5'), 128.1 (C5), 122.0 (C2', C6'), 120.1 (C4'); *m/z* (ESI) 343 ([^{81}Br]M$^+$, 20%), 341 ([^{79}Br]M+H$^+$, 40), 339 ([^{79}Br]M$^+$, 20), 282 (12). Found: M+H$^+$, 339.8847. $C_{12}H_8{}^{79/79}Br_2NO$ requires 339.8973. Anal Calcd for $C_{12}H_7Br_2NO$: C, 42.27; H, 2.07; N, 4.11. Found: C, 42.06; H, 1.93; N, 3.98.

(*E*)-3-Bromo-4-(phenylimino)cyclohexa-2,5-dien-1-one, 9a



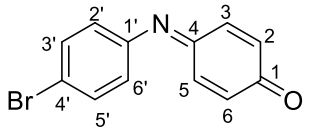
An orange oil, (0.46 g, 1.76 mmol, 32%), R_f = 0.81 (SiO_2 1:4 ethylacetate-petrol); IR υ_{max}/cm^{-1} (neat) 3199, 2918, 1596, 1492, 1467, 1227; ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.32 (2H, t, *J* 8.6 Hz, H3', H5'), 7.15 (1H, ddt, *J* 8.6, 7.4, 1.2 Hz, H4'), 7.13 (1H, d, *J* 2.2 Hz, H2), 7.02 (1H, d, *J* 10.2 Hz, H5), 6.79 (2H, d, *J* 8.6 Hz, H2', H6'), 6.42 (1H, dd, *J* 10.2, 2.1 Hz, H6); ^{13}C NMR ($CDCl_3$) δ 185.3 (C1), 153.1 (C4), 148.9 (C1'), 140.6 (C3), 136.0 (C2), 132.4 (C6), 129.2 (C3', C5'), 128.5 (C5), 126.6 (C4'), 120.4 (C2', C6'); *m/z* (ESI) 261 ([^{79}Br]M$^+$, 34%), 264 ([^{81}Br]M+H$^+$, 20%), 197 (14). Found: M+H$^+$, 261.9771. $C_{12}H_9{}^{79}BrNO$ requires 261.9868. Anal Calcd for $C_{12}H_8BrNO$: C, 54.99; H, 3.08; N, 5.34. Found: C, 54.83; H, 3.16; N, 5.24.

(*E*)-3-Bromo-4-((2,4-dibromophenyl)imino)cyclohexa-2,5-dien-1-one, 17a



An orange solid, (0.63 g, 1.5 mmol, 30%), R_f = 0.69 (RP 7:3 MeCN-H_2O); IR υ_{max}/cm^{-1} (neat) 3328, 2957, 2885, 1721, 1642, 1457, 1441, 1367, 1342, 1320, 1284; ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.76 (1H, d, *J* 2.0 Hz, H3'), 7.42 (1H, dd, *J* 8.4, 2.1 Hz, H5'), 7.21 (1H, d, *J* 2.1 Hz, H2), 6.86 (1H, d, *J* 10.2 Hz, H5), 6.58 (1H, d, *J* 8.4 Hz, H6'), 6.49 (1H, dd, *J* 10.2, 2.1 Hz, H6); ^{13}C NMR ($CDCl_3$) δ 184.9 (C1), 154.7 (C4), 146.5 (C1'), 139.8 (C3), 136.5 (C2), 135.7 (C3'), 133.0 (C6), 131.0 (C5'), 128.2 (C5), 121.2 (C6'), 119.4 (C4'), 115.3 (C2'); *m/z* (ESI) 423 ([^{81}Br]M$^+$, 58%), 422 (65), 421 (100), 419 (92), 417 ([^{79}Br]M$^+$, 36). Found 418.62. $C_{12}H_6{}^{79/79/79}Br_3NO$ requires 418.7979.

4-((4-Bromophenyl)imino)cyclohexa-2,5-dien-1-one, 11a



An orange oil, (0.09 g, 0.35 mmol, 7%), R_f = 0.73 (SiO_2 1:4 ethylacetate-petrol); IR υ_{max}/cm^{-1} (neat) 3312, 2959, 2931, 2872, 1779, 1713, 1654, 1591, 1476, 1373, 1304; ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.46 (2H, d, *J* 8.6 Hz, H3', H5'), 7.23 (1H, dd, *J* 10.1, 2.7 Hz, H3), 6.98 (1H, dd, *J* 10.3, 2.7 Hz, H5), 6.71 (2H, d, *J* 8.6 Hz, H2', H6'), 6.64 (1H, dd, *J* 10.1, 2.2 Hz, H2), 6.50 (1H, dd, *J* 10.3, 2.2 Hz, H6); ^{13}C NMR ($CDCl_3$) δ 187.5 (C1), 157.8 (C4), 148.1 (C1'), 141.2 (C3), 133.9 (C6), 133.1 (C2), 132.2 (C3', C5'), 127.9 (C5), 122.4 (C2', C6'), 119.9 (C4'). *m/z* (ESI) 264 ([^{81}Br]M+H$^+$, 55%), 262 ([^{79}Br]M+H$^+$, 48), 261 ([^{79}Br]M$^+$, 100).

Typical procedure for the addition of HCl to azaquinone **4** or azaquinone-*N*-oxide **16**

Conc. hydrochloric acid (37%, 1 mL) was added dropwise to a solution of azaquinone (1.0 g, 5.46 mmol) or azaquinone-*N*-oxide (1.0 g, 5.0 mmol) in acetic acid (75 mL). The solution was heated at reflux for 24 h when its colour changed from orange to blue. The reaction mixture was diluted with water (200 mL) and extracted with DCM (3 × 150 mL). The organic extracts were washed with water (3 × 50 mL), dried over sodium sulfate and stirred with lead (IV) acetate (8.0 g, 18 mmol) at RT for 1 h. The reaction mixture was then filtered to remove the oxidising agent and the solvent removed in vacuo to give the crude product.

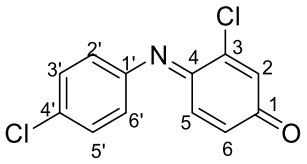
Azaquinone, **4** reaction with HCl

Purification by chromatography (SiO_2 1:4 ethylacetate-petrol) gave one major product, **9b.** Chlorination reaction with resorcinol also gave **9b**.

Azaquinone *N*-oxide, **16** reaction with HCl

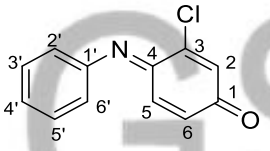
Purification by chromatography (SiO_2 1:9 ethylacetate-petrol) gave two products **10b** and **11b**. Chlorination reaction with resorcinol gave **9b** and **10b**.

(*E*)-3-Chloro-4-((4-chlorophenyl)imino)cyclohexa-2,5-dien-1-one, 10b



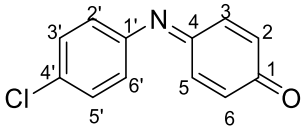
An orange solid, (0.88 g, 3.5 mmol, 70%), R_f = 0.74 (SiO_2 1:9 ethylacetate-petrol); Mp 80–82 °C (petrol-ethylacetate); IR υ_{max}/cm^{-1} (neat) 3372, 3058, 2960, 2872, 1701, 1640, 1575, 1479, 1383, 1364; ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.30 (2H, d, *J* 8.6 Hz, H3', H5'), 7.00 (1H, d, *J* 10.3 Hz, H5), 6.86 (1H, d, *J* 2.2 Hz, H2), 6.76 (2H, d, *J* 8.6 Hz, H2', H6'), 6.46 (1H, dd, *J* 10.2, 2.1 Hz, H6); ^{13}C NMR ($CDCl_3$) δ 185.7 (C1), 153.3 (C4), 147.0 (C1'), 132.6 (C6), 132.4 (C3), 131.7 (C2), 129.3 (C3', C5'), 128.3 (C5), 121.8 (C2', C6'), 120.4 (C4'); *m/z* (ESI) 253 ([^{37}Cl]M^+, 85%), 251 ([^{35}Cl]M^+, 100), 217 (60), 189 (50), 188 (70), 154 (88). Found: M+H$^+$, 251.9997. $C_{12}H_8{}^{35/35}Cl_2NO$ requires 251.9977.

(*E*)-3-Chloro-4-(phenylimino)cyclohexa-2,5-dien-1-one, 9b



An orange oil, (0.71 g, 3.28 mmol, 60%), R_f = 0.69 (SiO_2 1:9 ethylacetate-petrol); IR υ_{max}/cm^{-1} (neat) 3201, 1677, 1640, 1577, 1497, 1479, 1447, 1383, 1309; ^{1}H NMR 400 MHz (DMSO-d_6) δ 7.48 (2H, t, *J* 7.4 Hz, H3', H5'), 7.30 (1H, t, *J* 7.4 Hz, H4'), 7.14 (1H, d, *J* 2.1 Hz, H2), 7.09 (1H, d, *J* 10.2 Hz, H5), 6.97 (2H, d, *J* 8.6 Hz, H2', H6'), 6.62 (1H, dd, *J* 10.2, 2.1 Hz, H6); ^{13}C NMR (DMSO-d_6) δ 185.9 (C1), 153.1 (C4), 149.1 (C1'), 146.7 (C3), 132.9 (C6), 132.1 (C2), 129.7 (C3', C5'), 129.2 (C5), 126.8 (C4'), 120.8 (C2', C6'); *m/z* (ESI) 220 ([^{37}Cl]M+H$^+$, 100%), 219 (42), 218 ([^{35}Cl]M+H$^+$, 45), 185 (25). Found: M+H$^+$, 218.0355. $C_{12}H_9{}^{35}ClNO$ requires 218.0367.

4-((4-Chlorophenyl)imino)cyclohexa-2,5-dien-1-one, 11b



An orange oil, (0.13 g, 0.6 mmol, 12%), R_f = 0.50 (SiO_2 1:9 ethylacetate-petrol); IR υ_{max}/cm^{-1} (neat) 3365, 2961, 2935, 2874, 1645, 1595, 1491, 1458, 1364,1313; ^{1}H NMR

300 MHz ($CDCl_3$) δ 7.31 (2H, d, *J* 8.6 Hz, H3', H5'), 7.25 (1H, dd, *J* 10.1, 2.6 Hz, H3), 6.99 (1H, dd, *J* 10.1, 2.6 Hz, H5), 6.78 (2H, d, *J* 8.6 Hz, H2', H6'), 6.64 (1H, dd, *J* 10.0, 2.2 Hz, H2), 6.50 (1H, dd, *J* 10.0, 2.2 Hz, H6); ^{13}C NMR ($CDCl_3$) δ 187.5 (C1), 157.9 (C4), 147.4 (C1'), 141.5 (C3), 133.8 (C6), 133.0 (C2), 132.2 (C4'), 129.3 (C3', C5'), 127.9 (C5), 122.2 (C2', C6').*m/z* (ESI) 220 ($[^{37}Cl]M+H^+$, 96%), 219 (52), 218 ($[^{35}Cl]M+H^+$, 45), 217 (20). Found 217.03. $C_{12}H_8{}^{35}ClNO$ requires 217.0294.

Supporting Information

The Supporting Information is available.

Selected ^1H NMR, ^{13}C, ^1H-^1H COSY, HSQC and Crystallography data

Acknowledgments

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