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N-PHENYLQUINONEIMINE SULFONES IN THE SYNTHESIS OF PHENOXATHIIN

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ABSTRACT

N-Phenylquinoneimine compounds are an important class of reactive intermediates in synthetic organic chemistry. Their conjugated quinoneimine framework, combined with the electron-withdrawing influence of sulfone substituents, gives them unique electrophilic and redox properties. These characteristics make N-phenylquinoneimine sulfones valuable precursors in the preparation of sulfur-containing heterocyclic compounds, including Phenoxathiin. The aim of this study is to use N-phenylquinoneimine sulfones as essential intermediates in the synthesis of phenoxathiin providing an effective and distinct approach under mild reaction conditions instead of oxidising sulfur with potent oxidising reagents. N-Phenylquinoneimine sulfones were prepared from the reaction of N-phenylquinoneimine with sodium arenesulfinates. The cyclisation of the synthesized N-phenylquinoneimine sulfones using potassium tert-butoxide gave phenoxathiin dioxide in good yields. The N-phenylquinoneimine sulfones and phenoxathiin structures were confirmed by the ^{1}H NMR, ^{13}C NMR analysis and determination of the crystal structure. This methodology is very helpful in producing new phenoxathiin for a variety of uses due to its ease of synthesis. The development of efficient synthetic methodologies involving quinoneimine sulfones has significantly improved access to phenoxathiin derivatives with pharmaceutical and material-science applications.

Keywords: Drug discovery, *N*-phenylquinoneimine, organic synthesis, phenoxathiin, sulfones

INTRODUCTION

In organic chemistry, sulfones are useful synthetic intermediates and crucial building blocks for the creation of functional materials or biologically active compounds. Sulfone-containing molecules have been used in a variety of industries, including polymers, medicines, and agrochemicals [1-4]. In pharmaceutical chemistry, the sulfone scaffold is especially important. A sulfone unit is included in molecules used for a variety of medical purposes, such as the antimicrobial dapsone, bicalutamide, and eletriptan, which treat prostate cancer and migraines, respectively (Figure 1) [5].

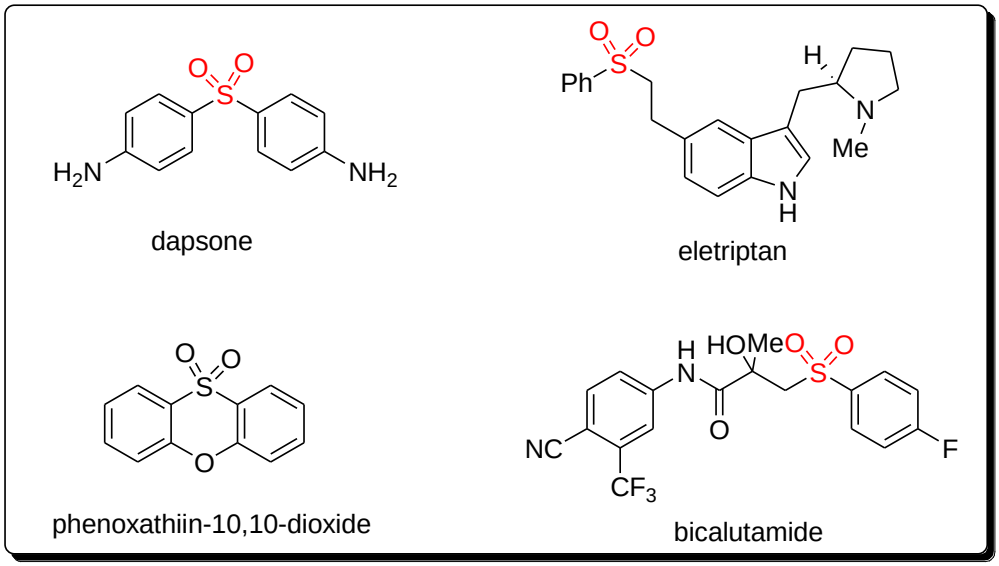


Figure 1: Some biologically active sulfone-containing compounds

Numerous medications and therapeutic candidates under research for the treatment of a wide range of illnesses affecting human health worldwide contain sulfones, which can be synthesised from multistep reactions of N-phenylquinoneimine [6]. Because of their exceptional strength and resistance to oxidation, corrosion, high temperatures, and creep under stress, certain polymers with sulfone groups are valuable engineering plastics. For instance, they can be used to replace copper in home hot water plumbing [7].

The sulfone functionality is especially important because it enhances the electrophilic nature of the molecule and can serve as a leaving group or directing group during ring-closure processes. Quinoneimine systems are also highly colored and chemically versatile, making them useful intermediates in heterocyclic synthesis which are essential in many natural products and drug-like molecules [8]. *O*-heterocyclic sulfones are phenoxathiin dioxides that have both a heterocyclic unit and a sulfone group (Figure 1).

In drug discovery research, aromatic heterocyclic compounds like phenoxathiins are frequently employed as scaffolding for creating combinatorial libraries [9]. A number of phenoxathiins, their oxides, dioxides, and halogen derivatives are recommended as intermediates, modifiers in plastic materials, and insecticides in dusts or sprays [10-11].

Heterocyclic sulfones have been reported to have application in organic electronic devices. The organic semiconductor material has the characteristics of structural diversity,

comparatively low manufacturing cost, excellent photoelectric performance, and has great potential in applications of photoelectric devices like light-emitting diodes (OLEDs) [12].

Heterocyclic sulfones have been identified as significant structural motifs in medicinal chemistry and drug discovery, as well as scaffolds in pharmaceutical compounds [13]. Methods for lowering the excipient load of pharmaceutical formulations with 3-fluoro-7-(2,2,2-trifluoroethoxy)phenoxathiin-10,10-dioxide as the active medicinal ingredient were published by Chen A. et al. [14].

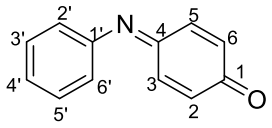
The aim of this study is to synthesize phenoxathiin via the intramolecular cyclization of N-phenylquinoneimine sulfones as an alternative route instead of the oxidation of sulfur compounds with strong oxidising reagents. Compared with older synthetic methods involving elemental sulfur and high temperatures, quinoneimine sulfone strategies provide cleaner reactions and greater structural diversity.

MATERIALS AND METHODS

A 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 NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz and 700 MHz spectrometers with residual protic solvent as an internal reference. Elemental analyses were carried out with the ThermoFlash 2000 analyzer at London Metropolitan University and are reported as the average of two runs. Melting points were recorded on a Gallenkamp MF-370 melting point apparatus and are uncorrected. *N*-phenylquinoneimine 1 was prepared according to a reported procedure [15].

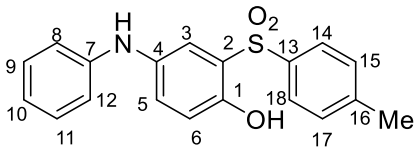
The crystal structure data for the synthesized compounds was collected on a Xcalibur, Atlas, Gemini ultra-diffractometer equipped with a fine-focus sealed X-ray tube ($\lambda_{CuK\alpha}$ = 1.54184 Å) and an Oxford Cryosystems CryostreamPlus open-flow N_2 cooling device. Cell refinement, data collection and data reduction were undertaken via software CrysAlisPro 1.171.38.42b (Rigaku Oxford Diffraction, 2015). Intensities were corrected for absorption using CrysAlisPro 1.171.38.42b. Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark et al. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. Using Olex2, the structure was solved using ShelXT and refined by XL.

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



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 the azaquinone 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.,[15] 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.

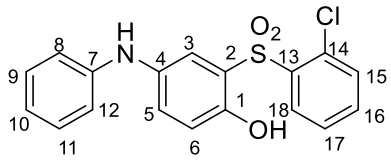
4-(Phenylamino)-2-tosylphenol, 3



Sodium 4-methylbenzenesulfinate (0.71 g, 4 mmol) was added in one portion to a solution of azaquinone (0.37 g, 2 mmol) in glacial acetic acid (20 mL) and heated to 70 °C. When the mixture turned colourless, it was cooled to room temperature and water was added until complete precipitation. The solid was filtered to give the crude product which was recrystallized from THF-petrol to give a colourless solid (0.67 g, 1.97 mmol, 98%), R_f = 0.43 (SiO_2 1:4 ethylacetate-petrol); Mp 104–106 °C (THF-petrol), lit.,[15] 82–84 °C (acetic acid); IR

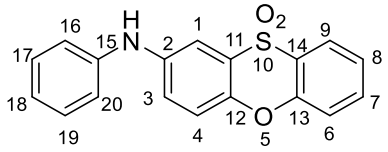
(neat) 3550, 3487, 3375, 2759, 1598, 1507, 1447, 1403 cm^{-1}; ^{1}H NMR 300 MHz (DMSO-d_6) δ 10.20 (1H, s, OH), 8.10 (1H, s, NH), 7.81 (2H, d, *J* 8.1 Hz, H14, H18), 7.67 (1H, d, *J* 2.8 Hz, H3), 7.39 (2H, d, *J* 8.1 Hz, H15, H17), 7.26 (1H, dd, *J* 8.0, 2.3 Hz, H5), 7.22 (2H, t, *J* 8.0 Hz, H9, H11), 6.97 (2H, d, *J* 8.1 Hz, H8, H12), 6.84 (1H, d, *J* 8.8 Hz, H6), 6.79 (1H, td, *J* 7.2, 1.2 Hz, H10), 2.37 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 149.9 (C1), 144.7 (C7), 144.1 (C16), 138.9 (C13), 135.5 (C4), 129.7 (C9, C11), 128.4 (C14, C18), 127.1 (C2), 126.4 (C5), 119.6 (C10), 118.9 (C6), 118.1 (C3), 116.6 (C15, C17), 115.9 (C8, C12), 21.5 (CH_3); *m/z* (ESI) 381 (45%), 340 ($M+H^+$, 100). Found: $M+H^+$, 340.1261. $C_{19}H_{18}NO_3S$ requires 340.1007. The crystal is monoclinic.

2-((2-Chlorophenyl)sulfonyl)-4-(phenylamino)phenol, 4



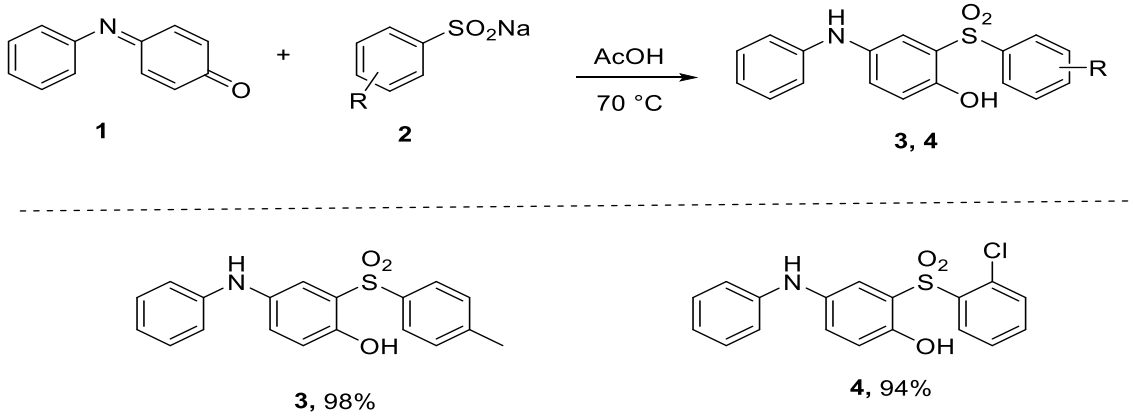
Sodium 2-chlorobenzenesulfinate (1.19 g, 6 mmol) was added in one portion to a solution of azaquinone (0.55 g, 3 mmol) in glacial acetic acid (30 mL) and heated to 70 °C. When the mixture turned colourless, it was cooled and water was added until complete precipitation. The solid was filtered to give the crude product which was recrystallized from THF-petrol to give a colourless solid (1.02 g, 2.84 mmol, 94%), R_f = 0.36 (SiO_2 1:4 ethylacetate-petrol); Mp 176–178 °C (THF-Petrol); IR (neat) 3375, 1596, 1515, 1486, 1449, 1402 cm^{-1}; ^{1}H NMR 700 MHz (DMSO-d_6) δ 10.20 (1H, s, OH), 8.27 (1H, dd, *J* 7.9, 1.8 Hz, H18), 8.11 (1H, s, NH), 7.74 (1H, d, *J* 2.9 Hz, H15), 7.69 (1H, td, *J* 7.7, 1.8 Hz, H17), 7.64 (1H, td, *J* 7.7, 1.3 Hz, H16), 7.59 (1H, dd, *J* 7.9, 1.3 Hz, H5), 7.29 (1H, dd, *J* 8.7, 2.9 Hz, H3), 7.22 (2H, t, *J* 7.7 Hz, H9, H11), 6.96 (2H, d, *J* 8.7 Hz, H8, H12), 6.84 (1H, d, *J* 8.7 Hz, H6), 6.78 (1H, tt, *J* 7.3, 1.1 Hz, H10); ^{13}C NMR (DMSO-d_6) δ 150.1 (C1), 144.9 (C7), 138.8 (C13), 135.4 (C17), 135.2 (C4), 132.5 (C18), 131.9 (C5), 131.3 (C14), 129.7 (C9, C11), 127.9 (C16), 127.4 (C3), 125.5 (C2), 119.8 (C15), 119.5 (C10), 118.7 (C6), 115.7 (C8, C12); *m/z* (ESI) 401 (62%), 362 ($[^{37}Cl]M^+$, 42%), 360 ($[^{35}Cl]M^+$, 100). Found: $M+H^+$, 360.0433. $C_{18}H_{15}{}^{35}ClNO_3S$ requires 360.0461. Anal Calcd for $C_{18}H_{14}ClNO_3S$: C, 60.08; H, 3.92; N, 3.89. Found: C, 59.89; H, 3.89; N, 3.70. The crystal is monoclinic.

2-(Phenylamino)phenoxathiine-10,10-dioxide, 5



Potassium tert-butoxide (0.67 g, 6 mmol) was added to a solution of **4** (1.0 g, 2.79 mmol) in DMF (20 mL) and heated to 90 °C for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with ethylacetate (3 × 150 mL). The organic products were combined, dried with $MgSO_4$ and the solvent removed in vacuo. Recrystallisation from THF gave **5** as colourless crystals (0.8 g, 2.46 mmol, 88%); R_f = 0.31 (1:4 ethylacetate-petrol); Mp 160–162 °C (THF); IR (neat) 3345, 2954, 1768, 1661, 1616, 1598, 1514, 1492, 1469, 1442, 1398, 1337 cm^{-1}; ^1H NMR 300 MHz (DMSO-d_6) δ 8.54 (1H, s, NH), 7.95 (1H, dd, *J* 8.2, 1.6 Hz, H9), 7.62 (1H, td, *J* 7.8, 7.4, 1.6 Hz, H8), 7.49 (1H, d, *J* 2.5 Hz, H1), 7.36 (1H, m, H3), 7.35 (1H, m, H7), 7.35 (1H, m, H6), 7.32 (1H, m, H4), 7.20 (2H, t, *J* 8.4 Hz, H3', H5'), 7.06 (2H, d, *J* 8.2 Hz, H2', H6'), 6.83 (1H, t, *J* 7.8 Hz, H4'); ^{13}C NMR (DMSO-d_6) δ 151.7 (C14), 144.2 (C11), 142.6 (C1'), 141.9 (C12), 135.0 (C8), 129.8 (C3', C5'), 125.3 (C7), 125.2 (C13), 124.3 (C2), 123.4 (C9), 123.3 (C6), 121.7 (C4'), 120.6 (C4), 119.3 (C3), 118.4 (C2', C6'), 106.9 (C1). *m/z* (ESI) 324 ($M+H^+$, 42%). Found: $M+H^+$, 324.0694. $C_{18}H_{14}NO_3S$ requires 324.0689. The crystal is monoclinic.

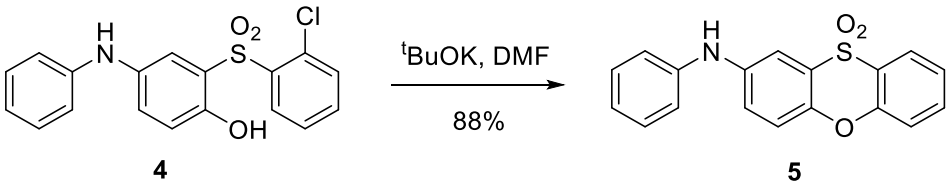
RESULTS AND DISCUSSION



Scheme 1: Synthesis of *N*-phenylquinoneimine sulfones

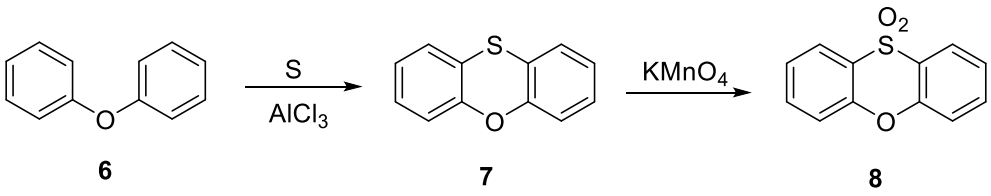
N-phenylquinoneimine **1** reacted with sodium arenesulfinates **2** to produce *N*-Phenylquinoneimine sulfones **3** and **4** (Scheme 1) [16, 17].

The reaction of *N*-phenylquinoneimine **1** with sodium arenesulfinates **2** was conducted by adding the sodium arenesulfinates to *N*-phenylquinoneimine in acetic acid, and the mixture was heated to 70 °C until it became colourless. After cooling, water was added until the solid completely precipitated. The product was removed by filtration, resulting in a 94-98% yield of sulfones.



Scheme 2: Synthesis of phenoxathiin dioxide from *N*-phenylquinoneimine sulfone

The cyclisation of *N*-phenylquinoneimine sulfones into phenoxathiin dioxide was then the focus of our study. Phenoxathiin dioxide **5** was obtained as colourless crystals in an 88% yield by adding potassium tert-butoxide to a solution of sulfone **4** in DMF at 90 °C for 24 h, then extracting the solid with ethylacetate and recrystallizing it from THF (Scheme 2). The new six-membered ring in **5** was formed by an intramolecular cyclisation reaction that followed a S_NAr interaction between the phenol and the chloroarene in **4**.



Scheme 3: Synthesis of phenoxathiin dioxide from diphenyl ether

Deasy C. L. reported a method of preparing phenoxathiin-10,10-dioxide [10]. Phenoxathiin dioxide **8** is formed when phenoxathiin **7** is oxidised by chromic acid, potassium permanganate, or by prolonged treatment with hydrogen peroxide, and obtained as colourless needles after recrystallization from dilute acetic acid [18, 19]. The Ferrario reaction [20], which occurs when diphenyl ether **6** and sulphur combine with anhydrous aluminium chloride, produced Phenoxathiin **7** (Scheme 3).

The cyclisation of *N*-phenylquinoneimine sulfone was considered as an alternative route to making phenoxathiin dioxide as part of multistep processes with mild reaction conditions versus the oxidation of sulphur with strong oxidising reagent.

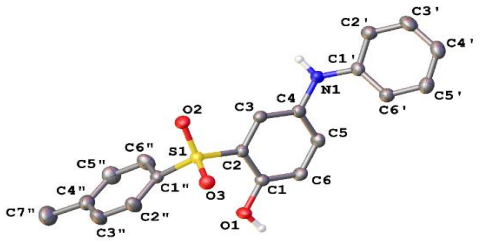


Figure 6: The crystal structure of compound **3**

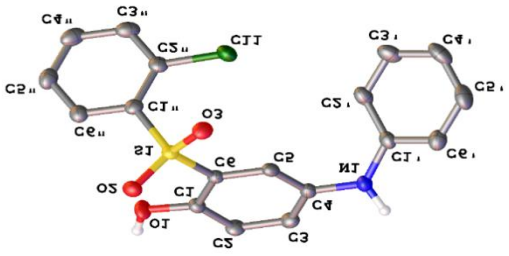


Figure 7: The crystal structure of compound **4**

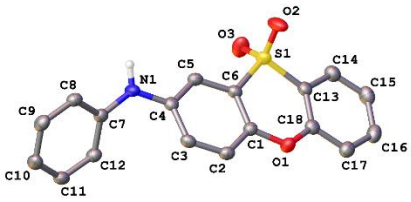


Figure 8: The crystal structure of compound **5**

Compounds **3, 4** and **5** were obtained as crystals after recrystallization from THF-petrol and confirmed by the ^{1}H NMR, ^{13}C NMR analysis and determination of the crystal structure. The crystal structures of compounds **3**, **4** and **5** are given in Figure 6, Figure 7 and Figure 8 respectively.

CONCLUSION

Sulfones are extensively utilised in organic synthesis, pharmaceuticals, agrochemicals and polymers. Numerous synthetic chemical compounds and therapeutic candidates with pertinent biological functions have the phenoxathiin motif. In conclusion, phenoxathiin has been produced using the oxidative cyclisation of *N*-phenylquinoneimine sulfone. There are still more phenoxathiin derivatives to be synthesised as scaffolds in medicinal compounds, as well as new innovative possibilities.

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