Regioselective Synthesis of Phenoxathiin Derivatives under Transition-Metal-Free Conditions

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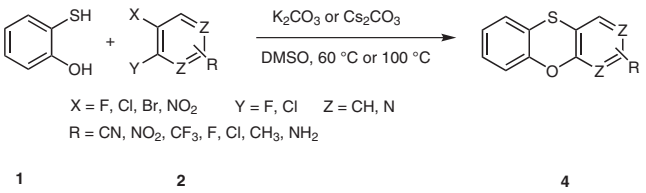
Abstract: A simple and efficient method was developed for the synthesis of phenoxathiin derivatives. A range of 1,2-dihaloarenes or 1-halo-2-nitroarenes reacted with 2-sulfanylphenol to give the desired products in good-to-excellent yields. It is intriguing that 1-halo-2-nitroarenes contaxining electron-donating groups worked well as substrates in this reaction.

Key words: regioselectivity, heterocycles, polycycles, cyclizations, fused-ring systems

Polycyclic fused heterocyclic derivatives can show a wide range of interesting biological activities, and some even have important applications in the drug industry. The polycyclic fused heterocycle phenoxathiin and its derivatives exhibit a variety of properties, including a range of biological activities,[1–7] fluorescence,[8,9] and electrochemical properties.[10,11] For example, phenoxathiin derivatives can be used as selective inhibitors of monoamine oxidase (MAO).[3] Sulfonylamido derivatives of 2-aminophenoxathiin display efficient antifungal activities.[5] In addition, some substituted phenoxathiins are strongly fluorescent.[8] Ionescu et al.[9] investigated the electronic and fluorescent properties of some 3-substituted phenoxathiin derivatives by experimental and theoretical methods. Furthermore, phenoxathiin derivatives have attracted a great deal of interest owing to stability of their cation radicals.[12–14]

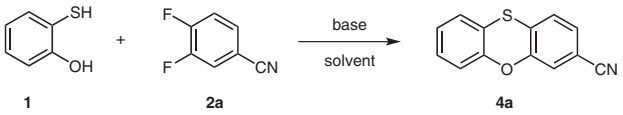
In an early report, Bennett described the synthesis of phenoxathiins from diphenyl ethers and sulfur as substrates in the presence of aluminum trichloride.[15] Eastmond and co-workers reported the use of cyano-activated fluoro-displacement reactions to give cyanophenoxazines and related compounds.[16] A number of other researchers have also reported syntheses of phenoxathiin derivatives.[17–21] Here, we describe a simple and efficient method for synthesizing a series of phenoxathiin derivatives that we hypothesized might be useful as fluorescent probes in pharmaceutical science. We used 2-sulfanylphenol and 1,2-dihaloarenes or 1-halo-2-nitroarenes as the substrates in dimethyl sulfoxide as the solvent with potassium carbonate as the base (Scheme 1).



Scheme 1 Synthesis of phenoxathiin derivatives

To determine the optimal conditions for the reaction, we used 2-sulfanylphenol and 3,4-difluorobenzonitrile as model substrates (Table 1). We initially chose potassium carbonate as the base with *N*,*N*-dimethylformamide, dimethyl sulfoxide, and acetonitrile as solvents, and we performed the reaction at room temperature. Of these solvents, dimethyl sulfoxide gave the highest yield (entry 2). Although high yields were obtained at room temperature, the reaction was relatively slow (entries 1–3), so we increased the temperature to 60 °C (entries 4–6), and again dimethyl sulfoxide gave the best results. We then examined the effects of various bases (entries 7–11), and

Table 1 Optimization of the Reaction Conditions



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	K_2CO_3	DMF	r.t.	41	57
2	K_2CO_3	DMSO	r.t.	24	82
3	K_2CO_3	MeCN	r.t.	24	trace
4	K_2CO_3	DMF	60	2.5	83
5	K_2CO_3	DMSO	60	3	90
6	K_2CO_3	MeCN	60	2.5	47
7	Na_2CO_3	DMSO	60	3	83
8	Cs_2CO_3	DMSO	60	2.5	87
9	Et_3N	DMSO	60	6.5	28
10	DBU	DMSO	60	3	89
11	$NaHCO_3$	DMSO	60	2.5	53

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we found that potassium carbonate was the most effective. The optimal reaction conditions therefore involve potassium carbonate as base and dimethyl sulfoxide as the solvent with the reaction being performed at 60 °C.

To continue our study, we treated a series of 1-halo-2-nitroarenes or 1,2-dihaloarenes with 2-sulfanylphenol under the optimized conditions. The desired products were obtained in good-to-excellent yields, and the results are shown in Table 2. It is noteworthy that 1,2-dihaloarenes or 1-halo-2-nitroarenes containing strong electron-withdrawing groups, such as cyano or nitro groups, gave high yields of the required products (entries 1–4), whereas 1,2-dichloro-4-nitrobenzene gave a lower yield from a slower reaction (entry 5). 1,2-Dihaloarenes or 1-halo-2-nitroarenes containing weak electron-withdrawing group also gave moderate yields of the required products (entries 6–8).

Table 2 Reactions of 2-Sulfanylphenol (**1**) with Various 1,2-Dihaloarenes or 1-Halo-2-nitroarenes **2**

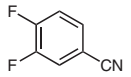
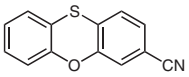
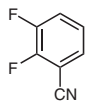
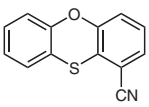
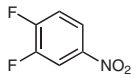
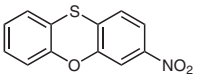
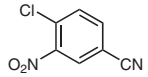
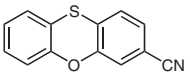
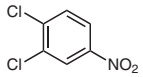
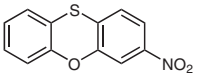
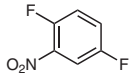
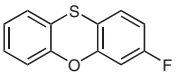
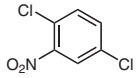
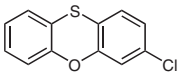
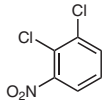
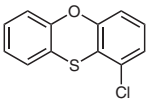
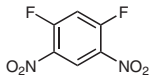
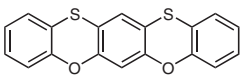
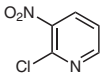
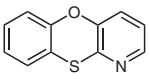
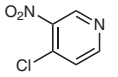
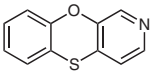
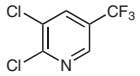
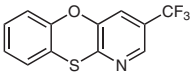
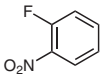
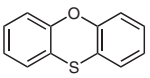
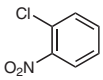
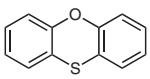
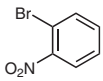
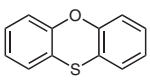
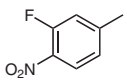
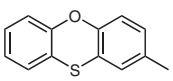
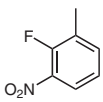
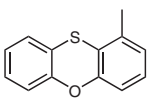
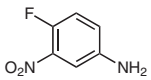
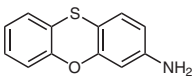
Entry	Substrate	Time (h)	Product	Yield[a] (%)
1[b]		3		90
	2a		**4a**	
2[b]		3		83
	2b		**4b**	
3[b]		1		92
	2c		**4c**	
4[b]		2		90
	2d		**4a**	
5[b]		23		61
	2e		**4c**	
6[b]		4		67
	2f		**4f**	
7[b]		5		77
	2g		**4g**	
8[b]		5		50
	2h		**4h**	

Table 2 Reactions of 2-Sulfanylphenol (**1**) with Various 1,2-Dihaloarenes or 1-Halo-2-nitroarenes **2** (continued)

Entry	Substrate	Time (h)	Product	Yield[a] (%)
9[b]		17		54
	2i		**4i**	
10[b]		2		74
	2j		**4j**	
11[c]		3		78
	2k		**4k**	
12[b]		3		55
	2l		**4l**	
13[d]		3		78
	2m		**4m**	
14[d]		3		81
	2n		**4m**	
15[d]		6		84
	2o		**4m**	
16[d]		11		57
	2p		**4p**	
17[d]		6		51
	2q		**4q**	
18[d]		2		54
	2r		**4r**	

[a] Isolated yield.
[b] Reaction conditions: **1** (1.2 mmol), **2a**–**r** (1 mmol), K_2CO_3 (2.5 mmol), DMSO (5 mL), 60 °C.
[c] Reaction conditions: **1** (1.2 mmol), **2a**–**r** (1 mmol), K_2CO_3 (2.5 mmol), DMSO (5 mL), 100 °C.
[d] Reaction conditions: **1** (1.2 mmol), **2a**–**r** (1 mmol), Cs_2CO_3 (2.5 mmol), DMSO (5 mL), 100 °C.

Substrates **2j**–**l** that contained a pyridine moiety could also be used in the reaction (entries 10–12). In addition, when three 1-halo-2-nitroarenes were examined as substrates, 2-bromo-1-nitrobenzene gave the corresponding

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product in a higher yield (84%) than the other two reactants (entries 13–15). The reaction of 1,5-difluoro-2,4-dinitrobenzene with 2-sulfanylphenol gave the symmetrical product **4i** in 54% yield (entry 9).

To extend the scope of reaction, we also examined the use of some 2-halo-1-nitroarenes containing an electron-donating group as substrates (entries 16–18). It is intriguing that the reaction also proceeded smoothly with these substrates to give the corresponding phenoxathiin derivatives in moderate yields. As can be clearly seen in Table 2, substrates **2** that possess a strong electron-withdrawing group worked well to give the desired products in high yields under relatively harsh conditions. Similarly, substrates **2** with no substituent group require the use of cesium carbonate as the base at 100 °C to give the corresponding products. From these result, it is clear that substrates **2** with electron-donating substituents and those lacking substituent groups need relatively higher temperatures and stronger bases to react. The structure of phenoxathiin-3-carbonitrile (**4a**) was confirmed by means of a single-crystal X-ray diffraction analysis (Figure 1).[22]

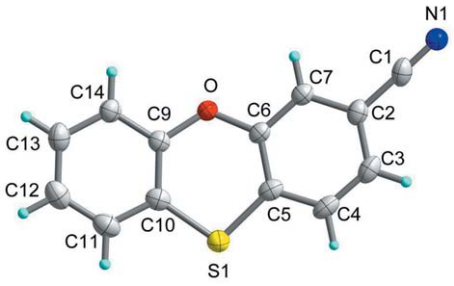
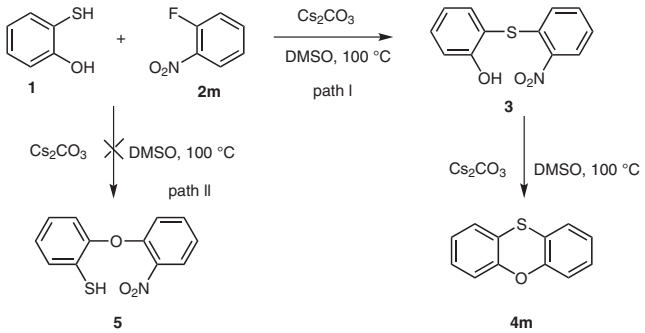


Figure 1 X-ray structure of phenoxathiin-3-carbonitrile (**4a**)

A plausible mechanism for the cyclization reaction is shown in Scheme 2. Reactants **1** and **2m** were chosen as model substrates to demonstrate the mechanism. First, 2-sulfanylphenol (**1**) gives a sulfur anion in the presence of cesium carbonate, and this anion subsequently forms the sulfide **3** through a nucleophilic substitution. The phenoxathiin is then formed through a second nucleophilic substitution reaction of sulfide **3**.



Scheme 2 A plausible mechanism for the reaction

In summary, we have developed a simple and effective route for synthesizing a series of phenoxathiin derivatives. A variety of 1,2-dihaloarenes and 1-halo-2-nitroarenes **2** reacted smoothly with 2-sulfanylphenol (**1**) to give the corresponding products in good-to-excellent yields. In this method, the electron-withdrawing group on the haloarene **2** plays a vital role in the first nucleophilic substitution step, so it is surprising that haloarenes **2** containing electron-donating groups worked well in the reaction and gave the desired products in moderate yields. Some of the phenoxathiin derivatives, such as phenoxathiin-3-carbonitrile (**4a**) and 3-nitrophenoxathiin (**4c**), exhibit fluorescent properties, so the products might be useful as fluorescent probes for use in biophotonic studies.

Commercial reagents were used as received without further purification. All reactions were conducted under N_2 and monitored by TLC. Melting points were determined on an XD-4 digital micro melting-point apparatus. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance 300 spectrometer with TMS as the internal standard and $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a Bruker Avance 300 (75 MHz) spectrometer with TMS as the internal standard and $CDCl_3$ as solvent. High-resolution mass spectra were recorded on an Agilent Q-TOF6510 spectrograph or a Bruker Apex IV FTMS spectrograph. IR spectra were recorded on a Nicolet 5MX-S infrared spectrophotometer. The single-crystal X-ray diffraction study was performed by using a Rigaku R-AXIS-SPIDER IP diffractometer operating at 50 kV and 20 mA. Data collection was performed at 273(2) K by using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å).

Phenoxathiin-3-carbonitrile (4a); Typical Procedure

Anhyd DMSO (5 mL) was added to a mixture of 2-HSC_6H_4OH (151 mg, 1.2 mmol), 3,4-$F_2C_6H_3CN$ (139 mg, 1.0 mmol), and K_2CO_3 (345 mg, 2.5 mmol) under N_2, and the mixture was stirred for 3 h at 60 °C. The mixture was then cooled to r.t. and extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with sat. brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, PE–CH_2Cl_2 (2:1)] to give white crystals; yield: 202 mg (90%); mp 142.6–143.4 °C.

IR (film): 753, 822, 883, 1472, 2222 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98–7.02 (m, 1 H), 7.04–7.08 (m, 2 H), 7.14–7.20 (m, 2 H), 7.21–7.22 (d, *J* = 1.5 Hz, 1 H), 7.25–7.28 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.94, 117.97, 120.74, 125.28, 126.77, 127.33, 127.51, 127.98, 128.48, 150.92, 151.94.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_8NOS$: 226.0321; found: 226.0334.

Phenoxathiin-1-carbonitrile (4b)

White solid; yield: 187 mg (83%); mp 99.4–100.5 °C.

IR (film): 737, 1288, 1429, 1439, 2232 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00–7.03 (m, 1 H), 7.04–7.10 (m, 1 H), 7.13–7.22 (m, 4 H), 7.33–7.36 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.53, 115.80, 117.71, 117.88, 121.75, 125.36, 125.89, 127.05, 127.80, 128.62, 128.82, 151.19, 152.58.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_8NOS$: 226.0321; found: 226.0318.

3-Nitrophenoxathiin (4c)

Yellow solid; yield: 225 mg (92%); mp 132.9–135.5 °C.

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IR (film): 737, 1225, 1345, 1463, 1511 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.00–7.03 (m, 1 H), 7.05–7.09 (m, 2 H), 7.16–7.21 (m, 2 H), 7.80–7.81 (d, *J* = 2.4 Hz, 1 H), 7.85–7.89 (dd, *J* = 2.4, 8.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.79, 117.49, 118.01, 119.46, 125.39, 126.64, 126.73, 128.66, 129.59, 150.65, 151.83.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_8NO_3S$: 246.0219; found: 246.0217.

3-Fluorophenoxathiin (4f)
Faint-yellow solid; yield: 146 mg (67%); mp 73.2–75.0 °C (Lit.[23] 77.5–79 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.72–6.79 (m, 2 H), 6.98–7.05 (m, 3 H), 7.08–7.17 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 106.47 (d, J_{CF} = 25.5 Hz), 112.10 (d, J_{CF} = 21.8 Hz), 115.75 (d, J_{CF} = 3.8 Hz), 118.29, 120.35, 125.36, 127.29, 127.70 (d, J_{CF} = 9.8 Hz), 128.32, 152.07, 153.59 (J_{CF} = 12.0 Hz), 162.74 (J_{CF} = 244.5 Hz).

3-Chlorophenoxathiin (4g)
White solid; yield: 181 mg (77%); mp 77.2–78.9 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.97–7.04 (m, 5 H), 7.06–7.10 (m, 1 H), 7.11–7.16 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.86, 118.25, 118.76, 119.49, 124.61, 124.87, 126.79, 127.25, 127.92, 132.93, 151.59, 152.62.

1-Chlorophenoxathiin (4h)
White solid; yield: 117 mg (50%); mp 92.5–93.9 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.85–6.88 (dd, *J* = 1.8, 7.5 Hz, 1 H), 6.94–7.00 (m, 2 H), 7.03–7.06 (m, 2 H), 7.08–7.15 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.41, 118.06, 119.24, 120.75, 125.25, 125.28, 127.35, 127.89, 128.55, 131.29, 151.65, 152.86.

[1,4]Benzoxathiino[3,2-*b*]phenoxathiin (4i)
White solid; yield: 174 mg (54%); mp 179.1–180.8 °C.

IR (film): 745, 871, 1224, 1457, 2924 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.72 (s, 1 H), 6.79 (s, 1 H), 6.97–6.99 (m, 1 H), 7.00–7.01 (m, 2 H), 7.03–7.10 (m, 3 H), 7.10–7.16 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.36, 116.22, 118.29, 120.07, 123.90, 125.20, 127.27, 128.30, 152.15, 152.21.

HRMS (ESI): *m/z* $[M^+]$ calcd for $C_{18}H_{10}O_2S_2$: 322.0117; found: 322.0115.

[1,4]Benzoxathiino[3,2-*b*]pyridine (4j)
White solid; yield: 149 mg (74%); mp 68.6–69.4 °C.

IR (film): 754, 1220, 1273, 1413, 1475 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.95–6.98 (m, 1 H), 7.01–7.05 (m, 2 H), 7.07–7.12 (m, 2 H), 7.15–7.18 (m, 1 H), 8.11–8.13 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.62, 119.08, 122.42, 123.82, 124.90, 127.09, 127.93, 143.65, 144.85, 148.07, 150.13.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_8NOS$: 202.0321; found 202.0317.

[1,4]Benzoxathiino[2,3-*c*]pyridine (4k)
White solid; yield: 157 mg (78%); mp 108.2–109.7 °C.

IR (film): 760, 821, 1277, 1404, 1469 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.98–7.06 (m, 4 H), 7.11–7.18 (m, 1 H), 8.14–8.16 (d, *J* = 5.1 Hz, 1 H), 8.20 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.75, 118.61, 121.28, 125.54, 127.35, 128.93, 131.13, 139.23, 145.59, 148.65, 151.60.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_8NOS$: 202.0321; found: 202.0318.

3-(Trifluoromethyl)[1,4]benzoxathiino[3,2-*b*]pyridine (4l)
White solid; yield: 148 mg (55%); mp 87.4–88.5 °C.

IR (film): 739, 754, 1115, 1164, 1332 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.96–6.98 (m, 1 H), 7.03–7.09 (m, 2 H), 7.13–7.17 (m, 1 H), 7.32 (d, *J* = 1.6 Hz, 1 H), 8.35 (d, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.68, 117.72, 120.3 (q, J_{CF} = 3.3 Hz), 122.85 (q, J_{CF} = 272.3 Hz), 125.42, 125.59 (q, J_{CF} = 33.6 Hz), 127.07, 128.45, 141.28 (q, J_{CF} = 4.4 Hz), 147.63, 148.71, 149.31.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_7F_3NOS$: 270.0195; found: 270.0192.

Phenoxathiin (4m)
White solid; yield: 156 mg (78%) from **2m**; 162 mg (81%) from **2n**; 168 mg (84%) from **2o**; mp 54.8–55.7 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.97–7.03 (m, 4 H), 7.08–7.15 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.28, 120.62, 125.00, 127.26, 128.19, 152.66.

3-Methylphenoxathiin (4p)
Yellow oil; yield: 122 mg (57%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 6.86–6.92 (m, 3 H), 6.95–7.01 (m, 2 H), 7.06–7.16 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.55, 117.42, 117.73, 119.61, 120.17, 124.31, 126.77, 127.03, 127.61, 128.24, 134.15, 149.94, 152.35.

1-Methylphenoxathiin (4q)
Colorless oil; yield: 109 mg (51%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 6.82–6.88 (m, 2 H), 6.95–7.02 (m, 3 H), 7.07–7.12 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.48, 115.29, 117.64, 119.92, 120.00, 124.39, 125.58, 126.78, 126.88, 127.76, 135.38, 151.92, 152.19.

Phenoxathiin-3-amine (4r)
Pale-brown solid; yield: 116 mg (**54**%); mp 90.5–91.5 °C (Lit.[24] 87–88 °C).

IR (film): 748, 1219, 1468, 2924, 3373 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 2 H), 6.36–6.39 (dd, *J* = 2.4, 8.1 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 6.85–6.87 (d, *J* = 8.1 Hz, 1 H), 6.96–7.01 (m, 2 H), 7.08–7.13 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.91, 107.73, 111.51, 117.72, 121.20, 124.31, 126.77, 127.26, 127.32, 146.65, 152.24, 153.27.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{10}NOS$: 216.0478; found: 216.0474.

2-[(2-Nitrophenyl)sulfanyl]phenol (3)
Yellow solid; yield: 210 mg (85%); mp 101.6–102.6 °C.

IR (film): 733, 1334, 1471, 1515, 3440 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 6.76–6.79 (dd, *J* = 1.2, 8.1 Hz, 1 H), 7.02–7.07 (m, 1 H), 7.12–7.15 (m, 1 H), 7.25–7.31 (m, 1 H), 7.36–7.42 (m, 1 H), 7.46–7.53 (m, 2 H), 8.27–8.30 (dd, *J* = 1.5, 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.96, 116.76, 122.50, 126.27, 126.69, 127.84, 133.98, 134.53, 136.74, 137.84, 145.97, 158.33.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{10}NO_3S$: 248.0376; found: 248.0376.

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(22) Crystallographic data for compound **4a** have been deposited with the accession number CCDC 890520, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.
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