A convenient synthesis of novel symmetrical bis-Schiff bases of 2, 2'-thio-bis[4-methyl(2-aminophenoxy)phenyl ether] in solution and under solvent-free conditions

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A convenient and straightforward procedure for the synthesis of novel symmetrical bis-Schiff bases has been achieved through the condensation of the symmetrical primary bis-amine 2,2'-thio-bis[4-methyl(2-aminophenoxy) phenyl ether] with a series of aryl aldehydes in organic solvents at room temperature and in solvent-free media, in moderate to high yields.

Keywords: bis-Schiff base, imine, bis-amine, solvent-free media, aldehyde

For many years particular attention has been paid to the synthesis and study of diimino-Schiff bases. Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds *via* ring closure, cycloaddition and replacement reactions.[1] Moreover, Schiff bases are also known to show biological activities such as antimicrobial[2-5] antifungal[6] and antitumor activity.[7] On the industrial scale, they have a wide range of applications such as their use as dyes and pigments.[8] Schiff bases have also been employed as chelating agents capable of coordinating metal ions to give complexes which serve as models for biological systems.[9,10]

Conventionally, Schiff bases have been prepared by refluxing mixtures of amines and carbonyl compounds in an organic solvent, for example ethanol or methanol,[11] but variations are known, such as treatment of the same mixture at room temperature, refluxing the mixture in heptane in the presence of acetic acid[12] or azeotroping the mixture with benzene in a Dean–Stark apparatus in the presence of acid[13] and by using a template procedure.[14]

In recent years, environmentally safer synthetic methods have received considerable attention and some solvent-free protocols have been developed. Catalysed synthesis of imines under solvent-free conditions may be carried out using microwave irradiation, ionic liquids, montmorillonite clays,[15] zeolites, silica, alumina or other matrices.[16] Particular attention has been paid to the synthesis and study of bis-imine Schiff bases because of their applications in metal ion complexation and their ability to act as inhibitors of human α-thrombin and as antimicrobial agents.[17-19]

In continuation of our interest in the synthesis of bis-imine Schiff bases, we now describe the synthesis of some novel symmetrical bis-Schiff bases from 2,2'-thio-bis[4-methyl (2-aminophenoxy)phenyl ether] (**1**) and aromatic aldehydes, by condensation reactions in solution and in thermal solvent-free conditions. Compound **1** has been synthesised already and used as a novel complexing agent for Cd^{+2} and Co^{+2} with no significant interference from other ions such as Zn^{+2} being observed.[20] Complexation studies of the Schiff base derivatives of this ligand with heavy metal ions are currently being studied in our laboratory.

As part of a continuous effort to develop new N,O,S-ligand derivatives relevant to bis-Schiff bases, we report two methods for the synthesis of novel bis-Schiff bases with bis-amine **1**, one in methanol in the presence of formic acid catalyst at room temperature and a second in solvent-free conditions, in almost quantitative yields. Our literature survey showed that bis-amine **1** has not previously been used for the synthesis of bis-Schiff base derivatives.

As the model reaction, we initially examined the reaction of bis-amine **1** and 2-hydroxy benzaldehyde, in methanol in the presence of formic acid catalyst at room temperature. It was found that at least 20 h is needed for the reaction to be completed. When this reaction was performed in solvent-free conditions at 70–120 °C in the absence of acid catalyst, the corresponding Schiff base was obtained. Our investigation demonstrated that the best result was obtained when temperature was fixed at 100 °C in which case the reaction was completed in 2 minutes. Therefore, we decided to examine the other reactions in solventless conditions at 100 °C in the absence of acid catalyst.

The bis-Schiff bases **3a–h** were synthesised by condensation of 2,2'-thio-bis[4-methyl (2-aminophenoxy)phenyl ether] (**1**) and aromatic aldehydes **2a–h** (2-hydroxy benzaldehyde, 5-bromo-2-hydroxy benzaldehyde, 2-hydroxy-5-nitro benzaldehyde, 4-choloro-3-nitro benzaldehyde, 3-indol carbaldehyde, 4-nitro benzaldehyde, 3-nitro benzaldehyde and 2-nitro benzaldehyde respectively) in methanol in the presence of formic acid catalyst at room temperature and solvent-free conditions at 100 °C for the appropriate time (Scheme 1).

Compounds **3a–h** were identified on the basis of spectroscopic data. The IR spectra of **3a–h** showed the characteristic C=N absorption bands at 1622, 1621, 1632, 1632, 1625, 1639, 1629 and 1619 cm^{-1}, respectively. The absorption band of NH in **3e** was observed at 3384 cm^{-1}. The hydroxyl absorption bands for **3a–c** absorbed weakly in their IR spectra because the hydroxyl groups were located at the *ortho*-position with respect to the imino-groups, which probably were involved in enol-keto tautomerisation processes. In the aliphatic region, the ^1H NMR spectra of **3a–h** show a singlet peak arising from CH_3 at about δ 2.20 ppm, hydroxyl protons of **3a–c** were presented as broad signals at about δ 13.50 ppm due to enol-keto tautomerisation and the remaining protons of the corresponding aromatic molecules and imine protons were presented in the aromatic regions. All of the products **3a–h** were pale-coloured powders and were analytically pure as isolated. Yields, melting points and reaction times are summarised in Table 1.

In summary, we have successfully developed a quick, convenient and efficient method for the synthesis of novel bis-Schiff base derivatives. Compared to other previously reported procedures in the literature, the solventless method has advantages such as omitting organic solvent, no need for a catalyst, generality and simplicity of procedure, easy product separation, lower reaction time, and high yields; merits to be

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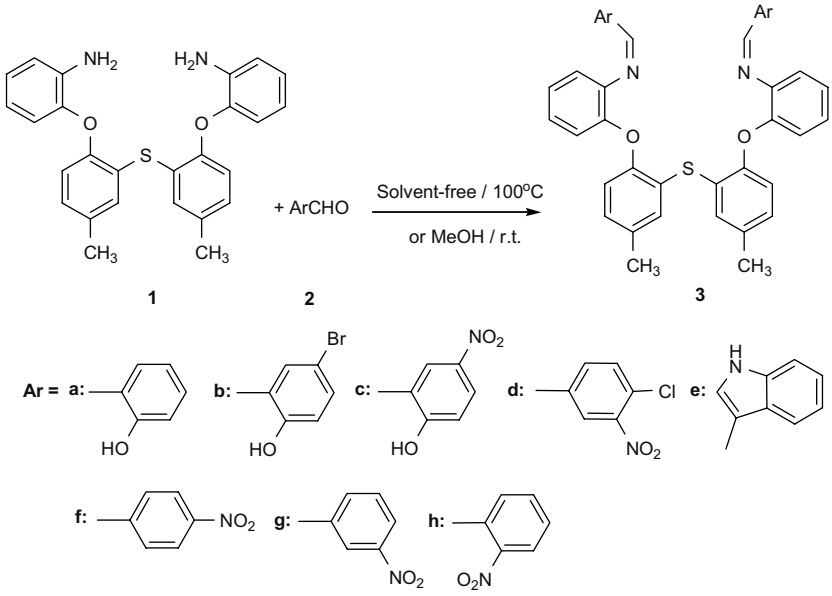
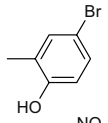
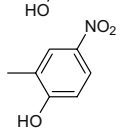
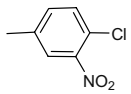
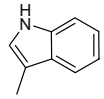
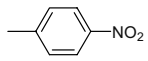
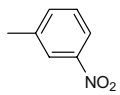


Scheme 1

Table 1 Reaction times, yields and melting points of the products **3** in CH_3OH and solventless condition

Products	Ar	CH_3OH (r.t.)		Solventless		Mp (°C)
		Time/h	Yield/%	Time/min	Yield/%	
3a		20	75	2	90	75–76
3b		15	80	2	92	188–190
3c		7	80	2	87	184–185
3d		25	72	5	89	169–171
3e		25	65	3	85	98–99
3f		15	78	3	90	178–180
3g		18	75	3	89	164–165
5h		16	80	4	92	139–140

recommended. The compounds **3a–h** are potential chelating agents for metal ions and this aspect is currently under study in our research laboratory.

Experimental

All commercially available chemicals and reagents were used without further purification. Melting points (uncorrected) were determined by an Electrothermal engineering LTD 9100 apparatus. IR spectra were recorded on a Perkin-Elmer model 543, the ^{1}H- and ^{13}C NMR spectra were obtained using Bruker Avance DRX 300 apparatus at 298 K. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent peak. Elemental analyses were carried out by a CHN–O-Rapid Heraeus elemental analyser (Wellesley, MA). Progress of the reactions was monitored by TLC using precoated sheets of silica gel Merck 60 F254 on aluminium.

General procedure for the synthesis of compounds **3a–h** *in methanol:* A solution of [2,2-thio-bis[4-methyl(2-aminophenoxy) phenyl ether] (**1**) (1.0 mmol), an aromatic aldehyde (2.0 mmol) and formic acid (0.005 g of 98% aqueous solution, 0.1 mmol), in methanol (40 mL) was stirred for the time given in Table 1 at room temperature. At the end of the reaction, water was added to the coloured solutions until solid products precipitated. The products were then filtered, washed with cold methanol, dried and purified by recrystallisation from EtOH–H_2O to give bis-Schiff bases **3** as crystals.

General procedure for the synthesis of compounds **3a–h** *in solvent-free conditions:* A mixture of compound **1** (1.0 mmol) and an aromatic aldehyde (2.0 mmol) was magnetically stirred on a preheated oil bath at 100 °C for the appropriate time as indicated in Table 1. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and ethanol–water (1 : 1) 10 mL was added until solid products precipitated. The precipitate was filtered, washed with cold ethanol, dried and purified by recrystallisation from EtOH–H_2O to give bis-Schiff base **3** as crystals.

2,2'-Thio-bis[2-(2-(4-tolyloxy)phenylimino)methyl)phenol] (**3a**): Yellowish crystals. IR (KBr): 1622 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ 2.19 (s, 6H, CH_3), 6.72–7.45 (m, 24H, ArH), 8.89 (s, 2H, imine-H), 13.14 (s, 2H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 20.61, 117.62, 119.54, 119.58, 119.61, 120.21, 121.57, 124.92, 126.08, 128.59, 130.32, 133.58, 133.90, 134.00, 134.91, 140.09, 150.91, 154.05, 162.12, 165.21. Anal. Calcd for $C_{40}H_{32}N_2O_4S$: C, 75.47; H, 5.03; N, 4.40. Found: C, 75.55; H, 5.10; N, 4.45%.

2,2'-Thio-bis[2-{2-(4-tolyloxy)(phenylimino)methyl}-5-bromophenol] (**3b**): Yellow crystals. IR (KBr): 1621 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 6H, CH_3), 6.76–7.37 (m, 20H, ArH), 8.63 (s, 2H, imine-H), 13.32 (broad, 2H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.69, 110.14, 118.40, 119.16, 119.30, 120.58, 122.16, 123.65, 125.49, 127.83, 129.56, 133.23, 134.27, 134.53, 135.58, 137.95, 149.80, 152.52, 160.35, 163.14. Anal. Calcd for $C_{40}H_{30}N_2Br_2O_4S$: C, 60.30; H, 3.77; N, 3.52. Found: C, 60.25; H, 3.65; N, 3.60%.

2,2'-Thio-bis[2-(2-(4-tolyloxy)phenylimino)methyl)-5-nitrophenol] (**3c**): Orange crystal. IR (KBr): 1632 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ 2.22 (s, 6H, CH_3), 6.80–8.48 (m, 20H, ArH), 9.15 (s, 2H, imine-H), 14.73 (s, 2H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 20.66, 118.85, 119.06, 119.24, 120.58, 121.23, 124.68, 126.48, 128.92, 129.58, 129.68, 130.53, 134.09, 135.58, 137.68, 140.43, 151.52, 153.53, 163.21, 168.22. Anal. Calcd for $C_{40}H_{30}N_4O_8S$: C, 66.11; H, 4.13; N, 7.71. Found: C, 65.95; H, 4.04; N, 7.75%.

2,2'-Thio-bis[N-(4-chloro-3-nitrobenzylidene)-2-(4-tolyloxy) benzamine] (**3d**): Yellowish crystals. IR (KBr): 1632 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ 2.14 (s, 6H, CH_3), 6.73–8.18 (m, 20H, ArH), 8.63 (s, 2H, imine-H). ^{13}C NMR (75 MHz, acetone-d_6): δ 20.54, 115.63, 118.60, 119.30, 122.58, 125.05, 125.48, 128.11, 128.70, 130.09, 130.27, 132.41, 133.45, 133.58, 134.44, 137.55, 142.81, 149.85, 154.48, 159.38. Anal. Calcd for $C_{40}H_{28}N_4Cl_2O_6S$: C, 62.90; H, 3.66; N, 7.34. Found: C, 62.95; H, 3.72; N, 7.41%.

2,2'-Thio-bis[N-((1H-indol-3-yl)methylene)-2-(4-tolyloxy) benzamine] (**3e**): Pink crystals. IR (KBr): 3423 (NH) and 1619 (C=N_{imine}) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.24 (s, 6H, CH_3), 4.39 (broad, 2H, NH), 6.55–7.14 (m, 26H, ArH and imine-H). ^{13}C NMR (75 MHz, acetone-d_6): δ 20.50, 112.24, 116.73, 117.17, 117.32, 117.49, 117.87, 120.47, 120.56, 121.74, 123.75, 124.95, 125.62, 125.69, 129.90, 130.13, 133.02, 133.55, 133.77, 140.69, 143.49, 154.80. Anal. Calcd for $C_{44}H_{34}N_4O_2S$: C, 77.42; H, 4.98; N, 8.21. Found: C, 77.38; H, 5.04; N, 8.30%.

2,2'-Thio-bis[N-(4-nitrobenzylidene)-2-(4-tolyloxy)benzamine] (**3f**): Yellow crystals. IR (KBr): 1632 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 6H, CH_3), 6.78–7.30 (m, 14H, ArH), 7.83 (d, 4H, J = 8.71 Hz, ArH), 8.15(d, 4H, J = 8.71 Hz, ArH) 8.60 (s, 2H, imine-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.04, 118.63, 120.06, 123.27, 124.07, 124.63, 125.12, 127.63, 129.62, 129.77, 133.19, 134.12, 142.05, 142.40, 148.78, 149.52, 153.75, 160.48. Anal. Calcd for $C_{40}H_{30}N_4O_6S$: C, 69.16; H, 4.32; N, 8.07. Found: C, 69.08; H, 4.22; N, 8.17%.

2,2'-Thio-bis[N-(3-nitrobenzylidene)-2-(4-tolyloxy)benzamine] (**3g**): Yellow crystals. IR (KBr): 1629 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 6H, CH_3), 6.78–8.49 (m, 22H, ArH), 8.57 (s, 2H, imine-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.01, 118.96, 119.78, 123.33, 123.78, 124.39, 125.34, 127.27, 129.60, 129.85, 133.23, 134.19, 134.57, 134.62, 138.39, 142.35, 148.78, 148.87, 153.62, 160.44. Anal. Calcd for $C_{40}H_{30}N_4O_6S$: C, 69.16; H, 4.32; N, 8.07. Found: C, 69.11; H, 4.38; N, 8.15%.

2,2'-Thio-bis[N-(2-nitrobenzylidene)-2-(4-tolyloxy)benzamine] (**3h**): Yellow crystals. IR (KBr): 1619 (C=N_{imine}) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 6H, CH_3), 6.77–8.04 (m, 22H, ArH), 8.90 (s, 2H, imine-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.01, 118.94, 119.90, 121.87, 124.51, 124.63, 124.93, 125.46, 127.62, 129.49, 130.06, 130.66, 131.30, 131.83, 133.41, 133.73, 142.86, 149.33, 154.21, 158.06. Anal. Calcd for $C_{40}H_{30}N_4O_6S$: C, 69.16; H, 4.32; N, 8.07. Found: C, 69.10; H, 4.40; N, 7.95%.

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