Synthesis of Novel Symmetrical bis-Schiff Bases of 5,5'-Methylenebis(2-aminothiazole)

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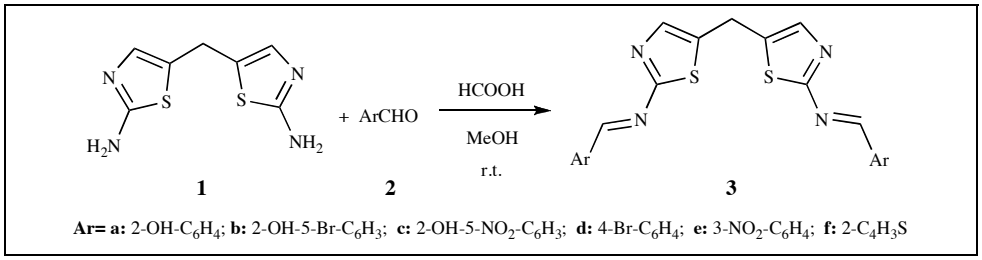

Novel symmetrical bis-Schiff bases have been prepared cleanly and efficiently in the presence of formic acid catalyst in methanol from the reaction of symmetrical primary bis-amine of 5,5'-methylenebis(2-aminothiazole) (**1**) and a series of aromatic aldehyde derivatives under mild conditions. The advantages of this reaction are simplicity of the reaction procedure, simple work-up and pure products with high yields. The structures of all the new synthesized symmetrical bis-Schiff bases were confirmed by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

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INTRODUCTION

Condensation of carbonyl compounds with primary amines was discovered in 1864 by Hugo Schiff [1]. This acid-catalyst reaction is universal and makes it possible to obtain a broad variety of azomethines. Schiff bases ligands, as variety of compounds with imine group have gained importance because of biological activities such as antimicrobial [2-5], antifungal [6], antitumor [7] and pharmacological activities associated with them. On the industrial scale, they have wide range of applications such as dyes and pigments [8]. They constitute an interesting class of chelating agents capable of metal complexation, which serves as models for biological system [9-11].

Conventionally Schiff bases have been prepared by refluxing mixtures of the amine and carbonyl compounds in an organic solvent (ethanol or methanol) [12]. Also the other reaction conditions were investigated for the synthesis of Schiff bases in the literature. For example, treatment of the above mixture has been studied at room temperature, refluxing in heptane as solvent in the presence of acetic acid as catalyst [13], or forming an azeotropic mixture of benzene and water in the presence of acid and using a Dean-Stark [14] apparatus to remove the water. Based on investigations in literature, it appears that the reaction of carbonyl compounds with bis-amine of 5,5'-methylenebis(2-aminothiazole) (**1**) [15] for the synthesis of symmetrical diimino Schiff bases have not been studied before.

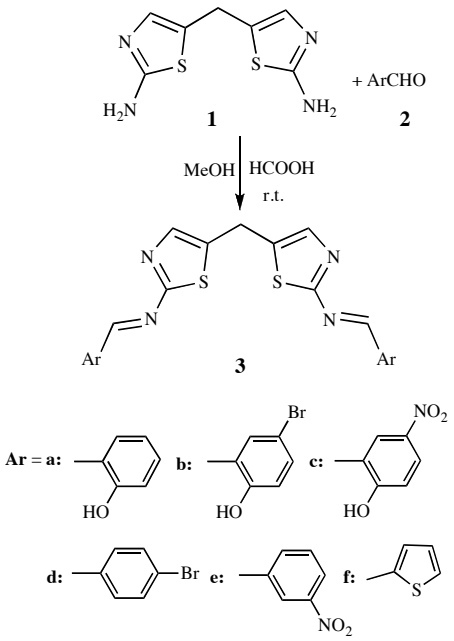
In the present paper, we report the synthesis of novel symmetrical bis-Schiff bases of diamine **1** and aromatic aldehyde derivatives **2** in the presence of formic acid catalyst in methanol under mild conditions. The complexing studies of Schiff base derivatives of this ligand with heavy metal ions are under study in our research laboratory.

RESULTS AND DISCUSSION

The bis-Schiff bases **3a-f** were synthesized by condensation of 5,5'-methylenebis(2-aminothiazole) (**1**) and aromatic aldehydes **2a-f** (2-hydroxy benzaldehyde, 5-bromo-2-hydroxy benzaldehyde, 2-hydroxy-5-nitro benzaldehyde, 4-bromo benzaldehyde, 3-nitro benzaldehyde and 2-thiophene carbaldehyde) by reaction in methanol and formic acid catalyst at room temperature (Scheme 1).

In the IR spectra of **3a-f** the characteristic C=N absorption bands appeared at 1626, 1594, 1610, 1631, 1599 and 1596 cm^{-1}, respectively. Hydroxyl absorption bands for **3a-c** were not absorbed in the IR spectra because the hydroxyl groups located at the *ortho* position with respect to the imino groups were involved enol-keto tautomerisation process when *ortho* and *para* hydroxyl derivatives of aromatic aldehydes were used. Hydroxyl protons of **3a-c** in ^{1}H NMR spectrum observed broad signals at δ 11.51, 11.52 and 10.28 ppm due to enol-keto tautomerisation, imine moiety appeared as a singlet signal in **3a-f** at about δ 9.1 ppm and remaining protons of the corresponding aromatic molecules showed in the aromatic regions. Mass spectra revealed the molecular ion peaks (M, M+2 and M+4) for compounds **3b** and **3d** with intensities 1:2:1 due to have two bromine atoms in these structures and other products exhibited the parent ions with medium intensity.

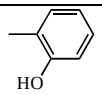
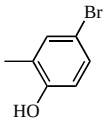
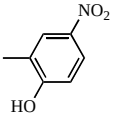
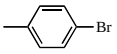
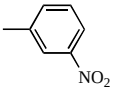
Scheme 1



The ion fragmentation of compounds **3a-f** is almost similar to each other. For example, ion fragmentation of compound **3e** is depicted in Scheme 2 as the representative common features of the parent ion decomposition.

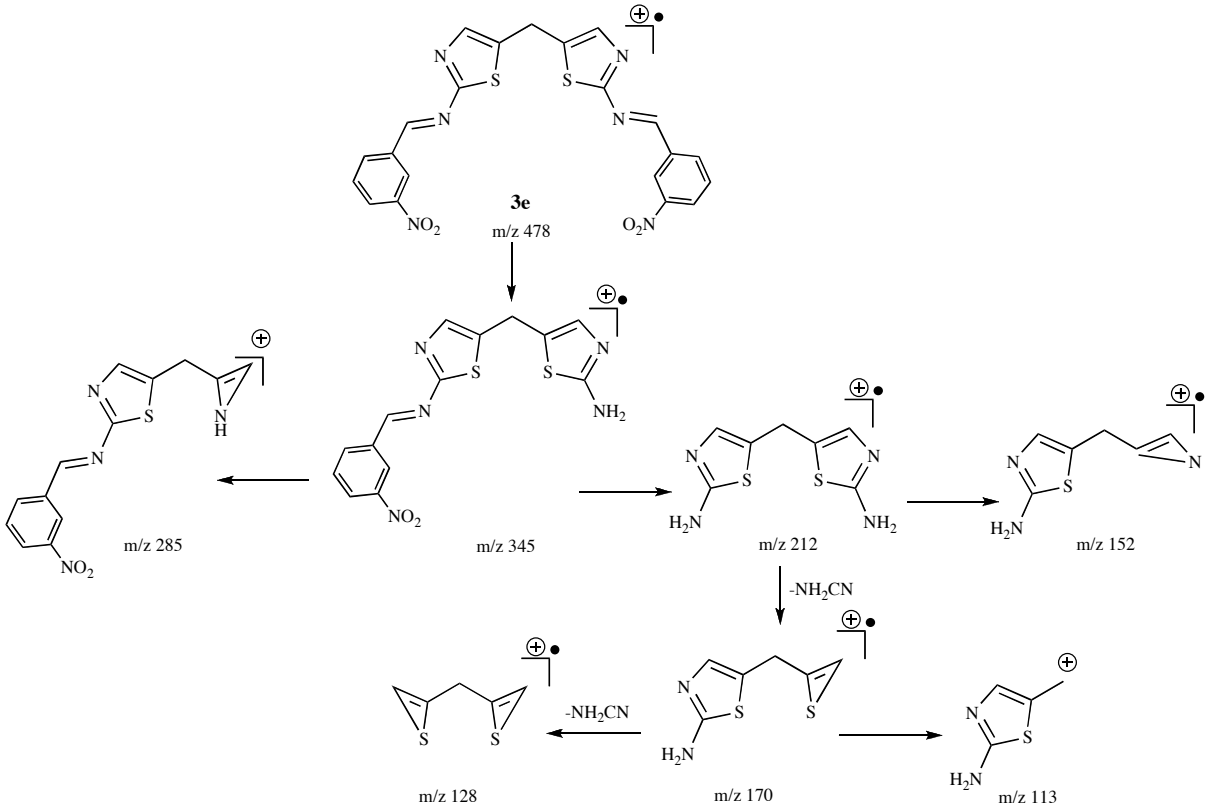
Table 1

Yields, melting points and reaction times of compounds **3a-f**

Entry	Ar	Time hours	Mp (°C)	Yield %	Color
3a		16	244-246	85	Yellowish
3b		20	265-267	83	Yellow
3c		12	258-260	90	Orange
3d		25	222-224	79	Yellow
3e		21	195-197	80	Yellow
3f		25	179-181	78	Yellow

All of the obtained products **3a-f** were colored powders and pure without purification. Yields, melting points and reaction times are presented in Table 1.

Scheme 2



In summery, the reaction between bis-amine **1** with aromatic aldehydes **2a-f** in methanol under mild conditions provides a series of novel symmetrical bis-Schiff bases **3a-f**. In this method, undesired products with low yields were very soluble in methanol and colored pure powders of desired products with high yields were obtained. The compounds **3a-f** as potential chelating agents for metal coordination is 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 analyzer (Wellesley, MA). Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. 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-f. A solution of 5,5'-methylenebis(2-aminothiazole) (1.0 mmole)**,** aldehydes **2a-f** (2.0 mmole), and formic acid (0.005 g of 98% aqueous solution, 0.1 mmole), in methanol (40 mL) was stirred at room temperature for the appropriate time (see Table 1). Water was then added to the colored solutions of **3d**, **3e** until a solid precipitated product was separated whereas in the reactions of **3a**, **3b, 3c** and **3f** the solid products were precipitated without water addition. The precipitates were filtered, washed with cold MeOH and dried.

5,5'-Methylenebis[2-(thiazol-2-ylimino)methyl)phenol] (**3a**). ir (potassium bromide): 1626 ($C=N_{imine}$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.48 (s, 2H, CH_2), 6.96, 7.45 and 7.81 (m, 8H, Ar-H), 7.61 (s, 2H, thiazol-H), 9.22 (s, 2H, imine-H), 11.50 ppm (s, 2H, OH); ^{13}C nmr (DMSO-d_6): δ 24.45, 116.78, 119.49, 119.73, 131.17, 134.88 135.25, 136.47, 139.21, 160.10, 163.14; ms: m/z 420 (M^+), 403, 316, 274, 241, 212, 159, 147, 132, 104; *Anal*. Calcd. For $C_{21}H_{16}N_4O_2S_2$: C, 60.00; H, 3.80; N, 13.33. Found: C, 59.91; H, 3.70; N, 13.36.

5,5'-Methylenebis[5-bromo-2-(thiazol-2-ylimino)methyl)-phenol] (**3b**). ir (potassium bromide): 1594 ($C=N_{imine}$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.51 (s, 2H, CH_2), 6.97, 7.60 and 7.99 (m, 6H, Ar-H), 7.64 (s, 2H, thiazol-H), 9.19 (s, 2H, imine-H), 11.52 ppm (s, 2H, OH); ^{13}C nmr (DMSO-d_6): δ 24.41, 122.21, 119.11, 121.63, 122.21, 131.87, 136.04, 136.70, 138.49, 158.91, 160.46, 160.75; ms: m/z 576 (M^+), 578 (M+2), 580 (M+4), 563, 561, 559, 396, 394, 379, 377, 354, 352, 321, 319, 239, 237, 225, 223, 212, 197, 182, 169, 155, 128, 103*; Anal*. Calcd. For $C_{21}H_{14}Br_2N_4O_2S_2$: C, 43.59; H, 2.42; N, 9.68. Found: C, 43.49; H, 2.50; N, 9.61.

5,5'-Methylenebis[5-nitro-2-(thiazol-2-ylimino)methyl)-phenol] (**3c**). ir (potassium bromide): 1610 ($C=N_{imine}$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.51 (s, 2H, CH_2), 7.14, 8.27 and 8.72 (m, 6H, Ar-H), 7.65 (s, 2H, thiazol-H), 9.28 (s, 2H, imine-H), 12.36 ppm (broad, 2H, OH); ^{13}C nmr (DMSO-d_6): δ 24.63, 117.77, 120.19, 125.29, 129.20, 137.26, 139.53, 139.89, 159.53, 164.90, 169.83; ms: m/z 510 (M^+), 493, 361, 344, 212, 192, 152, 128, 113; *Anal*. Calcd. For $C_{21}H_{14}N_6O_6S_2$: C, 49.41; H, 2.74; N, 16.47. Found: C, 49.35; H, 2.67; N, 16.37.

5,5'-Methylenebis[N-(4-bromobenzylidene)-2-amino thiazol] (**3d**). ir (potassium bromide): 1631 ($C=N_{imine}$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.50 (s, 2H, CH_2), 7.76 and 7.94 (dd, 8H, J = 8.52 Hz, Ar-H), 7.64 (s, 2H, thiazol-H), 9.01 ppm (s, 2H, imine-H); ^{13}C nmr (DMSO-d_6): δ 24.69, 126.56, 127.88, 131.22, 132.09, 133.80, 136.76, 139.28, 162.81; ms: m/z 543 (M^+), 545 (M+2), 547 (M+4), 381, 379, 377, 320, 318, 281, 279, 212, 200, 183, 170, 152, 128,113; *Anal*. Calcd. For $C_{21}H_{14}Br_2N_4S_2$: C, 46.15; H, 2.56; N, 10.25. Found: C, 46.10; H, 2.47; N, 10.29.

5,5'-Methylenebis[N-(3-nitrobenzylidene)-2-amino thiazol] (**3e**). ir (potassium bromide): 1599 ($C=N_{imine}$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.54 (s, 2H, CH_2), 7.69 (s, 2H, thiazol-H), 7.82-8.78 (m, 8H, Ar-H), 9.18 ppm (s, 2H, imine-H); ^{13}C nmr (DMSO-d_6): δ 24.54, 123.67, 126.80, 130.71, 135.25, 136.28, 137.45, 139.61, 148.26, 156.25, 162.07; ms: m/z 478 (M^+), 345, 285, 212, 170, 152, 128, 113; *Anal*. Calcd. For $C_{21}H_{14}N_6O_4S_2$: C, 52.72; H, 2.92; N, 17.57. Found: C, 52.65; H, 2.90; N, 17.50.

5,5'-Methylenebis[N-((thiophen-2-yl)methylene)-2-amino thiazol] (**4f**). ir (potassium bromide): 1596 ($C=N_{imine}$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.44 (s, 2H, CH_2), 7.26, 7.87 and 7.96 (m, 6H, Ar-H), 7.56 (s, 2H, thiazol-H), 9.14 ppm (s, 2H, imine-H); ^{13}C nmr (DMSO-d_6): δ 24.76, 128.92, 133.97, 136.13, 136.94, 139.10, 140.83, 156.69, 170.90; ms: m/z 400 (M^+), 334, 290, 246,231, 212, 154, 137, 128; *Anal*. Calcd. For $C_{17}H_{12}N_4S_4$: C, 51.00; H, 3.00; N, 14.00. Found: C, 50.98; H, 2.91; N, 14.09.

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