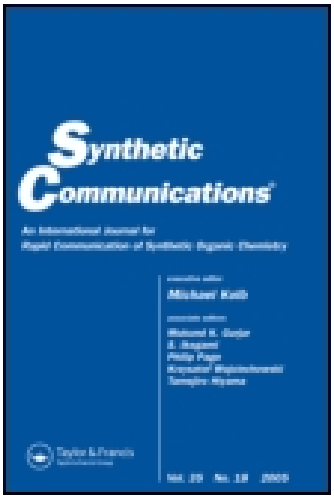

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Abbas Shockravi [a], Mahdieh Sadeghpour [b] & Abolfazl Olyaei [c]

[a] Faculty of Chemistry, Tarbiat Moallem University, Tehran, Iran

[b] Department of Chemistry, Islamic Azad University, Takestan Branch, Qazvin, Iran

[c] Department of Chemistry, Payame Noor University (PNU), Qazvin, Iran

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SIMPLE AND EFFICIENT PROCEDURE FOR THE SYNTHESIS OF SYMMETRICAL BIS-SCHIFF BASES OF 5,5′-METHYLENEBIS(2-AMINOTHIAZOLE) UNDER SOLVENT-FREE CONDITIONS

Abbas Shockravi,[1] Mahdieh Sadeghpour,[2] and Abolfazl Olyaei[3]

[1]*Faculty of Chemistry, Tarbiat Moallem University, Tehran, Iran*
[2]*Department of Chemistry, Islamic Azad University, Takestan Branch, Qazvin, Iran*
[3]*Department of Chemistry, Payame Noor University (PNU), Qazvin, Iran*

A simple and efficient procedure for the synthesis of symmetrical bis-Schiff bases has been described that employs a condensation reaction of symmetrical primary bis-amine of 5,5′-methylenebis(2-aminothiazole) with a series of aromatic aldehyde derivatives under solvent-free conditions at elevated temperature. The advantages of these reactions are simplicity of the reaction procedure, short reaction times, simple workup, catalyst-free conditions, and pure products in good to excellent yields. Details of the reaction conditions are discussed.

Keywords: Aldehyde; bis-amine; Schiff bases; solvent-free; symmetrical

INTRODUCTION

Organic reactions under solvent-free or so-called solventless conditions have gained in popularity in recent years.[1] This is because solvent-free reactions usually have shorter reaction times, simpler reactors, and simple and efficient workup procedures. The development of cleaner technologies is an important discussion in green chemistry. Among the several aspects of green chemistry, the reduction or replacement of volatile organic solvents from the reaction medium is the most important. The solid-state reaction or solvent-free reaction has many advantages: reduced pollution, low cost, and simplicity in process and handling. These factors are especially important in industry.[2]

Schiff base ligands are widely studied because of physiological, pharmacological, and medicinal activities.[3–5] They constitute an interesting class of chelating agents.[6–8] These complexes are used in some chemical processes as catalysts and also as biological models in understanding the structure of biomolecules and biological processes.[9–11]

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Address correspondence to Abbas Shockravi, Faculty of Chemistry, Tarbiat Moallem University, Mofatteh Ave., No. 49, Postal Code 15614, Tehran, Iran. E-mail: Abbas_shockravi@yahoo.co.uk

A variety of investigations have concerned the synthesis of Schiff bases, but these methods have some limitations such as use of a high-boiling-point volatile organic solvent, poor yields, long reaction times, and tedious workup procedures.[12,13] In recent years, synthetic methods have received considerable attention, and some solvent-free protocols have been developed. Catalyzed synthesis of imines under solvent-free conditions may be carried out by using microwave irradiation, ionic liquids, clays, zeolites, silica, alumina, or other matrices.[14]

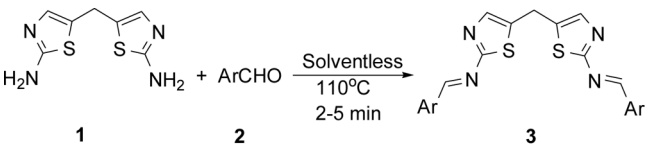
Particular attention has been paid to the synthesis and study of bis-imine Schiff bases because of their applications in metal ion complexation and because they can act as inhibitors of human α-thrombin and microbicides.[15–18] In continuation of our interest in the synthesis of bis-imine Schiff bases, we decided to synthesize some new bis-Schiff bases from 5,5′-methylenebis(2-aminothiazole)[19] and aromatic aldehydes using a condensation reaction under solvent- and catalyst-free conditions.

RESULTS AND DISCUSSION

We have previously reported a simple synthesis of bis-Schiff bases by condensation of 5,5′-methylenebis (2-aminothiazole) (**1**) and aromatic aldehydes (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.[20] This method has some limitations such as poor yields, methanol as organic solvent, formic acid as catalyst, and long reaction times. Based on these facts, we decided to synthesize these bis-Schiff bases and some new bis-Schiff bases of 5,5′-methylenebis(2-aminothiazole) cleanly and efficiently, without using any acid catalyst, in short reaction times under solventless conditions.

As the model reaction, we initially examined condensation of bis-amine (**1**) with 2-hydroxy benzaldehyde at 80–120 °C in the absence of acid catalyst. Our investigation demonstrated that the best result was obtained when temperature was fixed at 110 °C, in which the reaction was completed in 5 min. Therefore, we decided to examine the other reactions in solvent-free and catalyst-free conditions at 110 °C.

Bis-Schiff bases (**3a–l**) were prepared by combining 1 equivalent of bis-amine **1** with 2 equivalents of aromatic aldehydes (**2a–l**) in solventless conditions during 2–5 min at 110 °C (Scheme 1). These reactions require neither solvent nor inert atmosphere conditions. Each compound was isolated by the addition of ethanol to a cooled reaction mixture and filtration of the resulting precipitate in good to excellent yields. The results of these reactions are shown in Table 1.

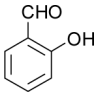
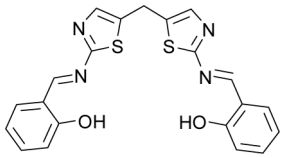
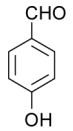
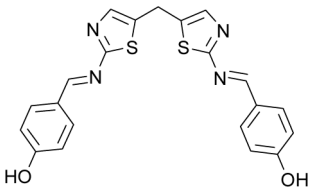
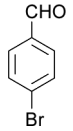
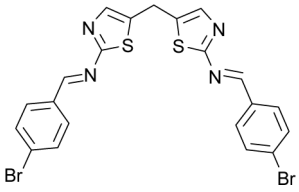
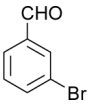
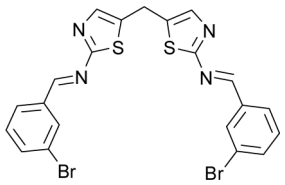
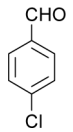
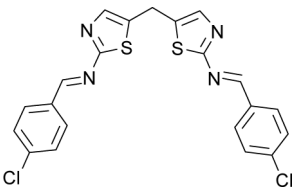
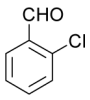
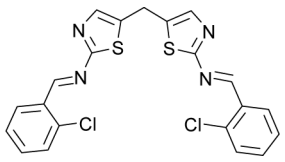
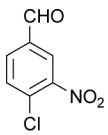
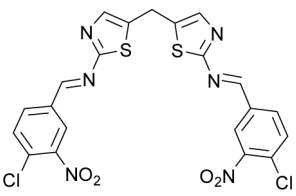


1 **2** **3**

Ar = **a:** 2-OH-C_6H_4, **b:** 4-OH-C_6H_4, **c:** 4-Br-C_6H_4, **d:** 3-Br-C_6H_4, **e:** 4-Cl-C_6H_4, **f:** 2-Cl-C_6H_4, **g:** 4-Cl-3-NO_2-C_6H_3, **h:** 2-OH-5-NO_2-C_6H_3, **i:** 2-OH-5-Br-C_6H_3, **j:** 3-NO_2-C_6H_4, **k:** 2-C_4H_3S, **l:** 3-C_8H_6N

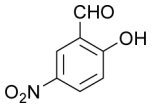
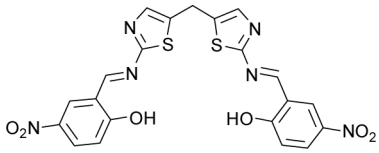
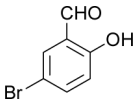
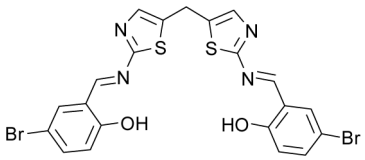
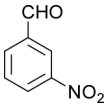
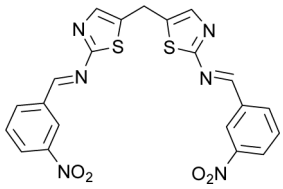
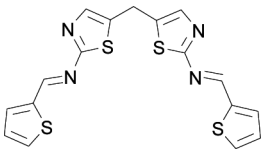
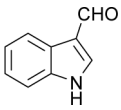
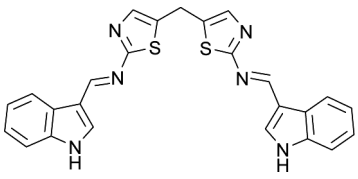
Scheme 1. Synthesis of symmetrical bis-Schiff bases of 5,5′-methylenebis(2-aminothiazole).

Table 1. Synthesis of bis-Schiff bases (**3a–l**) under solventless conditions

Entry	Aldehyde	Product	Time (min)	Yield (%)	Mp (°C) (lit.[ref.])
1			5	94	245–247 (244–246[19])
2			4	91	220–222
3			2	90	225–226 (222–224[19])
4			4	88	171–172
5			5	91	227–229
6			5	89	141–143
7			3	94	224–225

(*Continued*)

Table 1. Continued

Entry	Aldehyde	Product	Time (min)	Yield (%)	Mp (°C) (lit.[ref.])
8			3	95	259–261 (258–260[19])
9			2	92	268–269 (266–267[19])
10			3	88	194–196 (195–197[19])
11			2	85	182–183 (181–182[19])
12			3	92	260 (dec)

In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in good yields. This method can be compared with our previous work, which has occurred in solution.[20] It is concluded that the yields of Schiff base products in this method were better and that the reaction times were lower. Also, these reactions were carried out without a catalyst in solventless conditions.

The structure of new products has been assigned by spectroscopic data. In the infrared (IR) spectra, the characteristic Schiff base C=N stretching frequency is absorbed in the region $\upsilon = 1585$–$1615\,cm^{-1}$ as a strong band. In the ^1H NMR spectra, methylene protons are absorbed in the region $\delta = 4.42$–4.55 ppm, imine protons in the region $\delta = 8.84$–9.33 ppm, hydroxyl proton of compound **3b** at the region $\delta = 10.44$ ppm, NH proton of the compound **3l** at $\delta = 12.34$ ppm, and protons of aromatic rings at around $\delta = 6.91$–8.62 ppm. Mass spectra (MS) revealed the molecular ion peaks (M, M + 2, and M + 4) for compound **3d** with intensities 1:2:1 are due

to two bromine atoms in these structures, and other products exhibited the parent ions with medium intensity.

In conclusion, we have successfully developed a quick, convenient, efficient, and uncatalyzed method for the synthesis of bis-Schiff bases under solvent-free conditions. The environmental advantages include omitting organic solvent, generality and simplicity of procedure, shorter reaction time, simple workup, catalyst-free conditions, and pure products in good to excellent yields.

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, and the ^{1}H and ^{13}C NMR spectra were obtained using a Brucker Avance DRX 500 apparatus at 298 K. Chemical shifts (δ) are reported in parts per million and are referenced to the NMR solvent peak. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, Mass.). Mass spectra of the products were obtained with an HP (Agilent Technologies) 5937 mass selective detector. Progress of the reactions was monitored by thin-layer chromatography (TLC) using precoated sheets of silica gel (Merck 60 F254) on aluminium.

General Procedure: Synthesis of Bis-Schiff Bases 3a–l

A mixture of compound **1** (1 mmol) and an aromatic aldehyde (2 mmol) was magnetically stirred on a preheated oil bath at 110 °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 (10 mL) was added. Then the mixture was cooled to 0–5 °C. The precipitate was filtered, washed with cold ethanol, dried, and purified by recrystallization from EtOH to give bis-Schiff base **3** as colored crystals.

Selected Data

5,5′-Methylene-bis[4-(thiazol-2-ylimino)methyl)phenol] (3b). Yellow crystals; IR (KBr): 3369 (OH), 1592 ($C{=}N_{imine}$) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.42 (s, 2H, CH_2), 6.91 (d, 4H, J = 8.0 Hz, phenyl-H), 7.54 (s, 2H, thiazol-H), 7.85 (d, 4H, J = 8.0 Hz, phenyl-H), 8.84 (s, 2H, imine-H), 10.44 (s, 2H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.74, 116.89, 126.92, 132.90, 136.24, 136.85, 139.67, 164.12, 172.88 ppm; MS: m/z = 420 $[M]^+$, 405, 377, 262, 236, 212, 183, 152, 121, 97. Anal. calcd. for $C_{21}H_{16}N_4O_2S_2$: C, 60.00; H, 3.81, N, 13.33. Found: C, 60.10; H, 3.70, N, 13.38.

5,5′-Methylene-bis[N-(3-bromobenzylidene)-2-aminothiazol] (3d). Yellow crystals; IR (KBr): 1615 ($C{=}N_{imine}$) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.52 (s, 2H, CH_2), 7.49–8.17 (m, 8H, phenyl-H), 7.66 (s, 2H, thiazol-H), 9.01 (s, 2H, imine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.64, 123.16, 129.30, 132.10, 132.66, 136.16, 137.88, 137.97, 140.32, 159.80, 163.34 ppm; MS: m/z = 544 $[M]^+$,

546 $[M+2]^+$, 548 $[M+4]^+$, 379, 320, 226, 212, 196, 169, 152, 128. Anal. calcd. for $C_{21}H_{14}Br_2N_4S_2$: C, 46.15; H, 2.56; N, 10.25. Found: C, 46.18; H, 2.48; N, 10.36.

5,5′-Methylene-bis[N-(4-chlorobenzylidene)-2-aminothiazol] (3e). Yellow crystals; IR (KBr): 1601 ($C{=}N_{imine}$) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 4.51$ (s, 2H, CH_2), 7.63 (d, 4H, $J = 8.5$ Hz, phenyl-H), 7.64 (s, 2H, thiazol-H), 8.03 (d, 4H, $J = 8.5$ Hz, phenyl-H), 9.03 (s, 2H, imine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 25.52$, 114.55, 130.12, 132.06, 134.28, 137.70, 140.22, 163.62, 171.81 ppm; MS: $m/z = 457$ $[M]^+$, 334, 318, 274, 235, 182, 165, 150, 128. Anal. calcd. for $C_{21}H_{14}C_{l2}N_4S_2$: C, 55.14; H, 3.03; N, 12.25. Found: C, 55.19; H, 2.95; N, 12.34.

5,5′-Methylene-bis[N-(2-chlorobenzylidene)-2-aminothiazol] (3f). Yellow crystals; IR (KBr): 1585 ($C{=}N_{imine}$) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 4.53$ (s, 2H, CH_2), 7.49–8.19 (m, 8H, phenyl-H), 7.68 (s, 2H, thiazol-H), 9.33 (s, 2H, imine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 25.58$, 128.79, 129.61, 131.25, 132.30, 135.18, 136.95, 138.42, 140.51, 159.67, 171.61 ppm; MS: $m/z = 457$ $[M]^+$, 421, 352, 334, 318, 299, 284, 274, 224, 200, 182, 165, 150, 128. Anal. calcd. for $C_{21}H_{14}C_{l2}N_4S_2$: C, 55.14; H, 3.03; N, 12.25. Found: C, 55.05; H, 2.98; N, 12.16.

5,5′-Methylene-bis[N-(4-chloro-3-nitrobenzylidene)-2-aminothiazol] (3g). Yellow crystals; IR (KBr): 1598 ($C{=}N_{imine}$) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 4.55$ (s, 2H, CH_2), 7.70 (s, 2H, thiazol-H), 7.95–8.62 (m, 6H, phenyl-H), 9.13 (s, 2H, imine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 24.69$, 125.82, 128.60, 132.51, 133.73, 134.98, 137.63, 139.65, 147.89, 160.88, 170.11 ppm; MS: $m/z = 547$ $[M]^+$, 529, 379, 362, 319, 273, 227, 184, 152, 128. Anal. calcd. for $C_{21}H_{12}C_{l2}N_6O_4S_2$: C, 46.06; H, 2.19; N, 15.36. Found: C, 46.00; H, 2.10; N, 15.48.

5,5′-Methylene-bis[N-(1H-3-indolyl methylene)-2-aminothiazol] (3l). Orange crystals; IR (KBr): 3200 (NH), 1598 ($C{=}N_{imine}$) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 4.40$ (s, 2H, CH_2), 7.22–7.28, 7.52–8.30 (m, 10H, indol-H), 7.48 (s, 2H, thiazol-H), 9.07 (s, 2H, imine-H), 12.34 (s, 2H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 25.92$, 113.32, 115.04, 122.58, 122.74, 124.25, 125.41, 134.80, 138.09, 138.35, 139.22, 159.33, 174.55 ppm; MS: $m/z = 466$ $[M]^+$, 421, 368, 339, 313, 299, 285, 264, 236, 212, 152, 128. Anal. calcd. for $C_{25}H_{18}N_6S_2$: C, 64.37; H, 3.86; N, 18.02. Found: C, 64.25; H, 3.89; N, 18.10.

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