SYNTHESIS OF SOME NOVEL AND BIOLOGICALLY ACTIVE SCHIFF BASES BEARING A 1,3,4-THIADIAZOLE MOIETY UNDER ACIDIC AND PTC CONDITIONS

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ABSTRACT

The synthesis of some new Schiff bases bearing a 1,3,4-thiadiazole moiety, **3a-l**, by reaction of 2-amino-5-mercapto-1,3,4-thiadiazole with aromatic aldehydes under acidic and phase transfer catalyst (PTC) conditions was studied. The structure of all the Schiff bases was characterized using FT-IR and NMR spectroscopy, and elemental analyses. The antibacterial activity of these compounds was investigated against *Staphylococcus aureus* (RTCC, 1885), and *Escherichia coli* (ATCC, 35922).

Key words: Schiff base, 1,3,4-thiadiazole, biological activities, PTC

INTRODUCTION

There has been considerable attention to the chemistry of Schiff bases because of their wide range of applications in many fields including biological, organic, inorganic and analytical chemistry. They are used as pigments, dyes, catalysts, intermediates in organic and inorganic synthesis and polymer stabilizers.¹⁻⁴ Schiff bases containing heterocyclic rings are known to show cytotoxic, anticonvulsant, antimicrobial, anticancer, antifungal, antimalarial, antiviral, antidepressant and enzyme inhibitor activities.⁵⁻¹¹ Furthermore, some Schiff bases are used in ion sensors and electrochemical sensors to empower detection with enhanced selectivity and sensitivity.^{12,13}

Due to the importance and diverse structural aspects of Schiff bases, several methods and procedures have been reported for synthesis of these compounds.¹⁴⁻¹⁹ These methods usually involve the straightforward acid-catalyzed reaction of a primary amine and a carbonyl group in organic solvents. However, in spite of their advantages, most of them use procedures in which the chemical safety and yields of products are the main considerations. Hardly ever has attention been concentrated on the fact that some of these established methods use toxic solvents, special apparatus, or strong acid conditions. Consequently, in order to overcome these limitations, the introduction of more efficient methods for the synthesis of Schiff bases is still a challenge. Recently, significant research has been directed toward the solvent-free reaction in order to improve classical procedures and make them cleaner and easier to carry out.^{20,21} Keeping these reports in mind and also due to our interest in the synthesis of Schiff bases^{16,22-24} we wished to study the synthesis of some novel and biologically active Schiff bases bearing a 1,3,4-thiadiazole moiety under both solvent-free and acidic conditions.

EXPERIMENTAL

All reagents were commercially available without further purification. Melting points were determined with an Electrothermal WRS-1B apparatus. The IR spectra were recorded on a Galaxy FTIR 5000 spectrometer using KBr discs. The NMR spectra were recorded on a Bruker Avance spectrometer (300 MHz) using DMSO-*d*₆ as a solvent and TMS as an internal standard. Microanalyses were performed using the (Elemental, Vario EL III) Elemental Analyzer at Arak University. Reactions were monitored by thin layer chromatography (TLC) using silica gel F₂₅₄-coated aluminum sheets (Merck). The microbial strains, *Staphylococcus aureus* (RTCC, 1885) and *Escherichia coli* (ATCC, 35922) were obtained from the Pasteur Institute of Iran. The culture medium was Mueller Hinton Agar (MH).

Synthesis of Schiff bases **3a-l** with H₂SO₄

To a mixture of 2-amino-5-mercapto-1,3,4-thiadiazole **1** (0.133 g, 1 mmol) and corresponding aromatic aldehyde **2** (1 mmol) in ethanol (10 ml) was added 3-4 drops of concentrated sulfuric acid. The reaction mixture was refluxed for an appropriate time as presented in Table 1. After completion of the reaction, controlled by TLC, the reaction mixture was cooled to room temperature giving a solid product after 10-30 min, which was filtered and washed with a mixture of hot water and ethanol (1:1, 10 ml) to afford the pure product **3**.

Synthesis of Schiff bases **3a-l** with PTC

A mixture of 2-amino-5-mercapto-1,3,4-thiadiazole **1** (1 mmol), the corresponding aromatic aldehyde **2** (1 mmol) and benzyl triethylammonium chloride (BTEAC, 10 mol%) was heated in an oil bath at 90 °C for an appropriate time as presented in Table 1. The liquid mixture was cooled to room temperature to give a solid mass after 5-20 min, which was washed with H₂O/EtOH (1:1, 10 ml) to give the pure product **3**.

Antibacterial study

The agar diffusion test, or Kirby-Bauer disk-diffusion method was used for this purpose. Each chemically synthesized material (5 mg) was dissolved in 250 µl of DMSO and 100 µl of the solution of the test compounds was introduced onto the disks (0.7 cm diameter). The disks were then placed on top of the medium previously inoculated with the bacteria. 100 µl of solvent (DMSO) was added to another disk and implanted as a negative control on each plate along with the standard drugs. The plates were incubated overnight at 37°C. The inhibition zones were measured and compared with the controls. For the zone size interpretations were used recommendations of the National Committee of Clinical Laboratory Standards (NCCLS). The results are given in Table 2.

2-(Benzylideneamino)-5-mercapto-1,3,4-thiadiazole (3a). m.p 259-261 °C. IR (KBr): $\nu_{\max}$ 3043 (CH_{aromatic}), 1606 (C=N), 1572 (C=C). ¹H-NMR: δ_{H} 14.56 (s, 1H, S-H) 8.73 (s, 1H, CH=N), 7.68-7.45 (m, 5H, H_{aromatic}). ¹³C-NMR: δ_{C} 193.5 (C-N), 169.3 (C_{imine}), 135.0 (C-S), 130.4, 129.9, 129.5, 129.3 (CH_{arom}). Anal. Calcd for: C₉H₆N₂S₂, C, 48.85; H, 3.19; N, 18.99; S, 28.98%. Found: C, 48.65; H, 3.01; N, 19.18; S, 29.25%.

2-(2-Hydroxybenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3b). m.p 252-254 °C. IR (KBr): $\nu_{\max}$ 3070 (CH_{aromatic}), 1562 (C=N). ¹H-NMR: δ_{H} 14.54 (s, 1H, S-H) 11.14 (s, 1H, OH), 8.86 (s, 1H, CH=N), 7.86-6.95 (m, 4H, H_{aromatic}). ¹³C-NMR: δ_{C} 192.4 (C-N), 181.3 (CH_{aromatic}), 161.9 (C_{imine}), 161.1 (C-S), 136.8, 129.9, 122.6, 119.9, 117.6 (CH_{aromatic}). Anal. Calcd for: C₉H₆N₂OS₂, C, 45.55; H, 2.97; N, 17.71; S, 27.02%. Found: C, 45.60; H, 2.71; N, 17.95; S, 27.26%.

2-(2-Methoxybenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3c). m.p 148-149 °C. IR (KBr): $\nu_{\max}$ 3003 (CH_{aromatic}), 2937- 2835 (CH_{aliphatic}), 1599 (C=N). ¹H-NMR: δ_{H} 14.51 (s, 1H, S-H), 8.82 (s, 1H, CH=N), 7.78-7.00 (m, 4H, H_{aromatic}), 3.86 (s, 3H, CH₃). ¹³C-NMR: δ_{C} 189.5 (C-N), 187.0 (CH_{aromatic}), 163.4 (CH_{imine}), 160.9 (C-S), 136.4, 128.0, 122.3, 121.4, 112.8 (CH_{aromatic}), 56.5 (OCH₃). Anal. Calcd for: C₁₀H₆N₂OS₂, C, 47.79; H, 3.61; N, 16.72; S, 25.52%. Found: C, 47.96; H, 3.51; N, 16.51; S, 25.26%.

2-(2-Chlorobenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3d). m.p 242-244 °C. IR (KBr): $\nu_{\max}$ 3068 (CH_{aromatic}), 1560 (C=N). ¹H-NMR: δ_{H} 14.56 (s, 1H, S-H), 8.98 (s, 1H, CH=N), 7.68-7.46 (m, 4H, H_{aromatic}). ¹³C-NMR: δ_{C} 190.2 (C-N), 164.3 (CH_{imine}), 136.1 (C-S), 131.3, 131.1, 130.9, 130.0, 128.4, 128.3 (CH_{aromatic}). Anal. Calcd for: C₉H₅ClN₂S₂, C, 42.27; H, 2.36; N, 16.43; S, 25.08%. Found: C, 42.01; H, 2.30; N, 16.59; S, 25.28%.

2-(5-Bromo-2-hydroxybenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3e). m.p 254-255 °C. IR (KBr): $\nu_{\max}$ 3086 (CH_{aromatic}), 1612 (C=N), 1512 (C=C). ¹H-NMR: δ_{H} 14.57 (s, 1H, S-H), 11.28 (s, 1H, OH), 8.79 (s, 1H, CH=N), 7.98-6.96 (m, 3H, H_{aromatic}). ¹³C-NMR: δ_{C} 187.1 (C-N), 164.4 (CH_{aromatic}), 164.2 (CH_{imine}), 159.6 (C-S), 138.2, 131.4, 122.2, 119.8, 111.3 (CH_{aromatic}). Anal. Calcd for: C₉H₆BrN₃OS₂, C, 34.19; H, 1.91; N, 13.29; S, 20.28%. Found: C, 34.30; H, 2.21; N, 13.19; S, 20.16%.

2-(3-Bromobenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3f). m.p 235-237 °C. IR (KBr): $\nu_{\max}$ 3078 (CH_{aromatic}), 1568 (C=N), 1510 (C=C). ¹H-NMR: δ_{H} 14.62 (s, 1H, S-H), 8.72 (s, 1H, CH=N), 8.15-7.50 (m, 4H, H_{aromatic}). ¹³C-NMR: δ_{C} 192.3 (C-N), 137.4 (CH_{imine}), 136.8 (C-S), 132.4, 131.7, 129.9, 129.1, 128.6, 122.8 (CH_{aromatic}). Anal. Calcd for: C₉H₆BrN₃S₂, C, 36.01; H, 2.01; N, 14.00; S, 21.36%. Found: C, 36.14; H, 2.11; N, 14.09; S, 21.17%.

2-(4-Isopropylbenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3g). m.p 237-239 °C. IR (KBr): $\nu_{\max}$ 3092 (CH_{aromatic}), 2960 (CH_{aliphatic}), 1566 (C=N). ¹H-NMR: δ_{H} 14.53 (s, 1H, S-H), 8.68 (s, 1H, CH=N), 7.93-7.43 (m, 4H, H_{aromatic}), 3.02-2.87 (m, 1H, CH), 1.23- 1.21 (dd, 6H, CH₃). ¹³C-NMR: δ_{C} 193.0 (C-N), 169.0 (CH_{imine}), 130.7 (CH_{aromatic}), 130.2 (C-S), 127.6, 127.5, 127.2 (CH_{aromatic}), 34.1 (C-Mes), 23.8 (3CH₃). Anal. Calcd for: C₁₂H₁₃N₃S₂, C, 54.72; H, 4.97; N, 15.95; S, 24.35%. Found: C, 54.58; H, 4.83; N, 16.21; S, 24.49%.

2-(4-Dimethylaminobenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3h). m.p 246-248 °C. IR (KBr): $\nu_{\max}$ 3086 (CH_{aromatic}), 2893 (CH_{aliphatic}), 1591 (C=N). ¹H-NMR: δ_{H} 14.26 (s, 1H, S-H), 8.41 (s, 1H, CH=N), 7.81-6.79 (m, 4H, H_{aromatic}), 3.07 (s, 6H, CH₃). ¹³C-NMR: δ_{C} 186.0 (C-N), 167.6 (CH_{imine}), 154.4 (CH_{aromatic}), 132.8 (C-S), 121.5, 112.0, 111.4 (CH_{aromatic}), 65.0 (CH₃). Anal. Calcd for: C₁₁H₁₂N₄S₂, C, 49.97; H, 4.58; N, 21.19; S, 24.26%. Found: C, 49.78; H, 4.49; N, 21.36; S, 24.14%.

2-(4-Nitrobenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3i). m.p 259-261 °C. IR (KBr): $\nu_{\max}$ 3014 (CH_{aromatic}), 1610 (C=N), 1568 (C=C), 1521, 1352 (NO₂). ¹H-NMR: δ_{H} 14.71 (s, 1H, S-H), 8.87 (s, 1H, CH=N), 8.40- 8.22 (m, 4H, H_{aromatic}). ¹³C-NMR: δ_{C} 181.3 (C-N), 167.5 (CH_{imine}), 131.5 (CH_{aromatic}), 130.1 (C-S), 128.8, 124.6, 124.0 (CH_{aromatic}). Anal. Calcd for: C₉H₆N₄O₂S₂, C, 40.59; H, 2.27; N, 21.04; S, 24.08%. Found: C, 40.71; H, 2.35; N, 21.19; S, 24.17%.

2-(4-Benzyloxybenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3j). m.p 215-217 °C. IR (KBr): $\nu_{\max}$ 3036 (CH_{aromatic}), 2982 (CH_{aliphatic}), 1610 (C=N), 1568 (C=C). ¹H-NMR: δ_{H} 14.46 (s, 1H, S-H), 8.62 (s, 1H, CH=N), 7.95-7.00 (m, 9H, H_{aromatic}), 5.22-5.15 (d, 2H, CH₂). ¹³C-NMR: δ_{C} 186.9 (C-N), 168.3 (CH_{imine}), 165.3 (CH_{aromatic}), 163.4 (C-S), 136.7, 132.7, 128.9, 128.5, 128.3, 127.5, 115.9 (CH_{aromatic}), 70.1 (CH₂). Anal. Calcd for: C₁₇H₁₄N₃OS₂, C, 58.69; H, 4.00; N, 12.83; S, 19.59%. Found: C, 58.83; H, 4.11; N, 12.61; S, 19.77%.

2-(4-Chlorobenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3k). m.p 222-224 °C. IR (KBr): $\nu_{\max}$ 3016 (CH_{aromatic}), 1610 (C=N), 1564 (C=C). ¹H-NMR: δ_{H} 14.50 (s, 1H, S-H), 8.74 (s, 1H, CH=N), 7.67-7.47 (m, 4H, H_{aromatic}). ¹³C-NMR: δ_{C} 187.0 (C-N), 168.1 (CH_{imine}), 138.8 (C-S), 133.4, 131.9, 129.8, 129.4 (CH_{aromatic}). Anal. Calcd for: C₉H₆ClN₃S₂, C, 42.27; H, 2.36; N, 16.43; S, 25.08%. Found: C, 42.09; H, 2.50; N, 16.11; S, 25.24.

2-(4-Fluorobenzylideneamino)-5-mercapto-1,3,4-thiadiazole (3l). m.p 233-234 °C. IR (KBr): $\nu_{\max}$ 3009 (CH_{aromatic}), 1606 (C=N), 1564 (C=C). ¹H-NMR: δ_{H} 14.54 (s, 1H, S-H), 8.73 (s, 1H, CH=N), 8.09- 7.38 (m, 4H, H_{aromatic}). ¹³C-NMR: δ_{C} 187.2 (C-N), 168.1 (CH_{imine}), 167.4 (C_{aromatic}, $J_{\text{C-F}}$ = 240.1 Hz), 133.4 (C-S), 133.0 (C_{aromatic}, $J_{\text{C-F}}$ = 3.0 Hz), 129.6 (C_{aromatic}, $J_{\text{C-F}}$ = 7.4 Hz), 116.7 (C_{aromatic}, $J_{\text{C-F}}$ = 20.1 Hz). Anal. Calcd for: C₉H₆FN₃S₂, C, 45.17; H, 2.53; N, 17.56; S, 26.80%. Found: C, 45.30; H, 2.47; N, 16.21; S, 25.09.

RESULTS AND DISCUSSION

The synthetic route for the preparation of the target compounds is outlined in Scheme 1.

Scheme 1. Preparation of Schiff bases 3a-l

Reaction of 2-amino-5-mercapto-1,3,4-thiadiazole **1** with corresponding aromatic aldehyde **2** under acidic conditions or in the presence of BTEAC catalyst afforded 5-mercapto-1,3,4-thiadiazole Schiff bases **3a-l**. The reaction was carried out with different aromatic aldehydes bearing electron-withdrawing groups (such as nitro, halide), or electron-releasing groups (such as methyl, NMe₂). The results are summarized in Table 1.

Table 1. Synthesis of Schiff bases **3a-l** under acidic and solvent free conditions.

Entry	R	Product ^a	Time ^b (min)	Yield ^b (%)	Time ^c (min)	Yield ^c (%)
1	H	3a	30	65	20	80
2	2-OH	3b	20	71	10	89
3	2-OMe	3c	60	40	30	61
4	2-Cl	3d	60	56	----	----
5	2-OH, 5-Br	3e	40	40	30	72
6	3-Br	3f	20	65	20	75
7	4-Isopropyl	3g	30	40	20	71
8	4- NMe ₂	3h	30	56	10	95
9	4- NO ₂	3i	45	30	30	65
10	4- OCH ₂ Ph	3j	60	38	----	----
11	4-Cl	3k	40	33	35	53
12	4-F	3l	----	----	30	83

^a All compounds form yellow crystals except for **3d** and **3h** which are white and orange, respectively.

^b catalyzed by H₂SO₄.

^c catalyzed by BTEAC.

The good yields of products, the use of safe and mild reaction conditions and the shorter reaction time are some advantages of the method for the synthesis of Schiff bases in the presence of BTEAC as compared to that carried out with sulfuric acid.

IR and NMR spectra data as well as elemental analyses are consistent with the expected structures. In the ¹H NMR spectra of all the Schiff bases synthesized here, the appearance of singlets at 8.41-8.98 and 14.26-14.71 ppm related to the resonance of vinyl and SH protons, respectively, is good evidence for the expected reactions. Also, In the IR spectra of compounds **3a-l** the absence of the absorption related to the NH₂ group of the starting material is in support of the reactions having taken place.

The antibacterial screening data revealed that none of the compounds showed antibacterial activity against *E. coli*, as an example of gram negative bacteria (Table 2). Compounds **3b-j** and **3l** showed good inhibition against *S. aureus* comparable to penicillin. Also, the anti-*S. aureus* activity of compounds **3c**, **3e** and **3h** is better than that of the other compounds.

Table 2: Inhibition zone diameter for Schiff bases **3a-l**.

Entry	Compounds	<i>S. aureus</i> (mm)	<i>E. coli</i> (mm)
1	3a	—	—
2	3b	15±0.1	—
3	3c	25±0.2	—
4	3d	7±0.1	—
5	3e	32±0.2	—
6	3f	9±0.1	—
7	3g	8±0.2	—
8	3h	29±0.2	—
9	3i	17±0.1	—
10	3j	17±0.1	—
11	3k	—	—
12	3l	9±0.1	—
13	DMSO	—	—
Gentamicin 18mm	10 U Penicillin 33 mm	Standard drugs	

— indicates resistance of bacteria to compounds. The inhibition zone numbers are the averages of three independent experiments.

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References

1. a) D. N. Dhar, C. L. Taploo, J. Sci. Ind. Res. 41, 501 (1982). b) H-B. Zhu, Z-Y. Dai, W. Haung, K. Cui, Sh-H. Gou, Ch-J. Zhu, Polyhedron. 23, 1131 (2004). c) M. Salavati-Niasari, E. Zamani, M. Bazarganipour, Applied Clay. Sci, 38, 9 (2007). d) M. Colak, N. Demirel, Tetrahedron-Asymmetr. 19, 635 (2008).
2. N. Yoshikawa, M. Shibasaki, Tetrahedron. 58, 8289, (2002).
3. a) W. Radecka-Paryzek, V. Patroniak, J. Lisowski, Coord. Chem. Rev. 249, 2156 (2005). b) M.Y. Khuhawar, M. A. Mughal, A. H. Channar, Eur. Polym. J. 40, 805 (2004). c) K. C. Gupta, A. K. Sutar, Ch. Lin, Coord. Chem. Rev. 253, 1926 (2009).
4. C. Spînu, M. Pleniceanu, C. Tigae, Turk. J. Chem. 32, 487, (2008).
5. N. Nishat, Sh. Parveen, S. Dhyani, Asma, T. Ahamad.. J. Appl. Polym. Sci. 113, 1671 (2009).
6. Y-Y. Yu, H-D. Xian, J-F. Liu, G-L. Zhao, Molecules, 14, 1747 (2009).
7. A. Jarrahpour, D. Khalili, E. De.Clercq, C. Salmi, J. M. Brunel, Molecules. 12, 1720 (2007).
8. a) M. A. Ali, A. H. Mirza, R. J. Butcher, M. T. H. Tarafder, T. B. Keat, A. M. Ali, J. Inorg. Biochem. 92, 141 (2002). b) G. B. Bagihalli, P. G. Avaji, S. A. Patil, P. S. Badami, Eur. J. Med. Chem. 43, 2639 (2008).
9. Z. L. You, D. H. Shi, Ch. Xu, Q. Zhang, H. L. Zhu, Eur. J. Med. Chem. 43, 862 (2008).
10. a) N. Rahman, S. Johnson Raja, J. Joseph, A. Sakthivel, J. Dhavethu Raj, J. Chil. Chem. Soc. 53, 1599, (2008). b) T. Sethi, A. Chaturvedi, R. K. Upadhyay, S. P. Mathur, J. Chil. Chem. Soc. 52, 1206 (2007).
11. Z-L. You, D-H. Shi, H-L. Zhu, Inorg. Chem. Commun. 9, 642 (2006).
12. M. Parra, S. Hernandez, J. Alderete, J. Chil. Chem. Soc. 48 (2003).
13. S. E. Ibrahim, A. Sharif, E-J. Chem. 4, 531 (2007).
14. J. E. dos Santos, E. R. Dockal, E. T. G. Cavaleiro, Carbohydr. Polym. 60, 277 (2005).
15. H. Naeimi, J. Safari, A. Heidarneshad, Dyes Pigments. 73, 251 (2007).
16. A. Mobinikhaledi, P. J. Steel, M. Polson, Synth. React. Inorg. M. 39, 189 (2009).
17. H. Khanmohammadi, H. Salehifard, M. H. Abnosi, J. Iran. Chem. Soc. 6, 300 (2009).
18. C. Ma, J. Sun, R. Zhang, D. Wang. J. Organomet. Chem. 692, 4029 (2007).
19. R. Zhang, Q. Wang, Q. Li, C. Ma. Inorg. Chim. Acta. 362, 2762 (2009).
20. A. Louri, Top. Curr. Chem. 206, 153 (1999).
21. A. Mobinikhaledi, N. Foroughifar, J. Alipour Safari, E. Amini, J. Heterocyclic Chem. 44, 697 (2007).
22. A. Mobinikhaledi, N. Foroughifar, M. Kalhor, Turk. J. Chem. 34, 367 (2010).
23. A. Mobinikhaledi, N. Foroughifar, M. Kalhor, S. Ebrahimi, Eur. J. Chem. 1, 33 (2010).
24. A. Mobinikhaledi, M. Kalhor, L. Taheri, Asian J. Chem. 22, 7399 (2010).