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One Pot Synthesis and Characterization of Some Novel Schiff Bases with 1,3,4-Thiadiazole Unit

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A series of novel benzimidazole substituted Schiff bases were synthesized by the reaction of aromatic aldehydes with the corresponding ethyl acetoacetate or methyl acetoacetate and 1,3,4-thiadiazole. These compounds have been characterized by ^{1}H NMR, IR and mass spectra.

Keywords: Schiff bases, 1,3,4-Thiadiazole, Aromatic aldehydes.

INTRODUCTION

Schiff bases are an important class of organic compounds widely used in the manufacture of medicinal and pharmaceutical products. Thus, development and synthesis of novel Schiff base derivatives as potential chemotherapeutics attracts much attention of organic and medicinal chemists[1]. Schiff bases, derived mostly from various heterocyclic compounds, were reported to possess a wide variety of biological activities including antiviral[2], anticancer[3], cytotoxic[4], antimicrobial[5], antibacterial[6,7] and anticonvulsant[8]. Besides their potential application as biologically active agents, Schiff bases constitute one of the most relevant synthetic ligand systems in asymmetric catalysis[9]. New optical and organic conducting materials and polymers can be prepared by Schiff bases. Benzimidazole and its derivatives have potential uses as therapeutics because the benzimidazole nucleus is a very important pharmacophore in modern drug discovery and a constituent of vitamin B12. Thus it is not surprising that benzimidazoles display diverse biological activities such as antimicrobial[10,11], antifungal, antitumor[12-14], antiviral[15,16] antihistaminic[17] *etc*. Benzimidazole and its derivatives have been additionally found applications in several other areas such as optical laser and polymer dyes in optoelectronics[18], organic luminophores, fluorescent tags for detection of biological important molecules such as DNA, RNA or proteins and enzymes. These considerations prompted us to explore the synthesis of a new series of benzimidazole substituted Schiff bases with different aromatic rings as well as different substituent on the benzimidazole nuclei. The synthesis and spectroscopic characterization are reported here.

EXPERIMENTAL

All chemicals were of reagent grade, purchased from commercial sources and used without further purification. Aromatic aldehydes, ethyl acetoacetate phosphorus oxychloride and hydrazine were purchased from Aladdin Chemical Company and were used without further purification. All the solvents were dried using standard methods before use. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 400 for $CDCl_3$ solutions. X4-digital melting point reader was used to determine the melting points. Mass spectra were obtained on a LCQ DECA XP (Thermo Company). Elemental analyses were performed in a Fash-1112 instrument.

In order to synthesize the following 9 novel Schiff bases 1,3,4-thiadiazole derivatives were designed and synthesized *via* the route as shown in Fig. 1.

Synthesis of 5-phenyl-1,3,4-thiadiazol-2-amine (3): A stirring mixture of benzoic acid (50 mmol), N-aminothiourea (50 mmol) and $POCl_3$ (13 mL) was heated at 75 °C for 0.5 h. The reaction mixture was cooled down to room temperature and add amount of water. The reaction mixture was refluxed for 4 h and cooled; the mixture was basified to pH 8 by the dropwise addition of 50 % NaOH solution under stirring[19]. The precipitate was filtered and recrystallized with ethanol to yield 7 g (79.1 %) of the title compound **3** as white solid; m.p.: 224-226 °C; IR (KBr, ν_{max}, cm^{-1}): 3276, 3114 (t N-H), 1634 (t C=N), 691 (t C-S); ^{1}H NMR (DMSO-d_6): δ 7.40 (s, 2H), 7.43-7.49 (dd, J = 6.38 Hz, J = 14.00 Hz, 2H), 7.74-7.76 (d, J = 6.94 Hz, 2H).

Synthesis of compound 5 *i.e.*, (2Z,3E)-methyl 3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)-2-benzylidenebutanoate

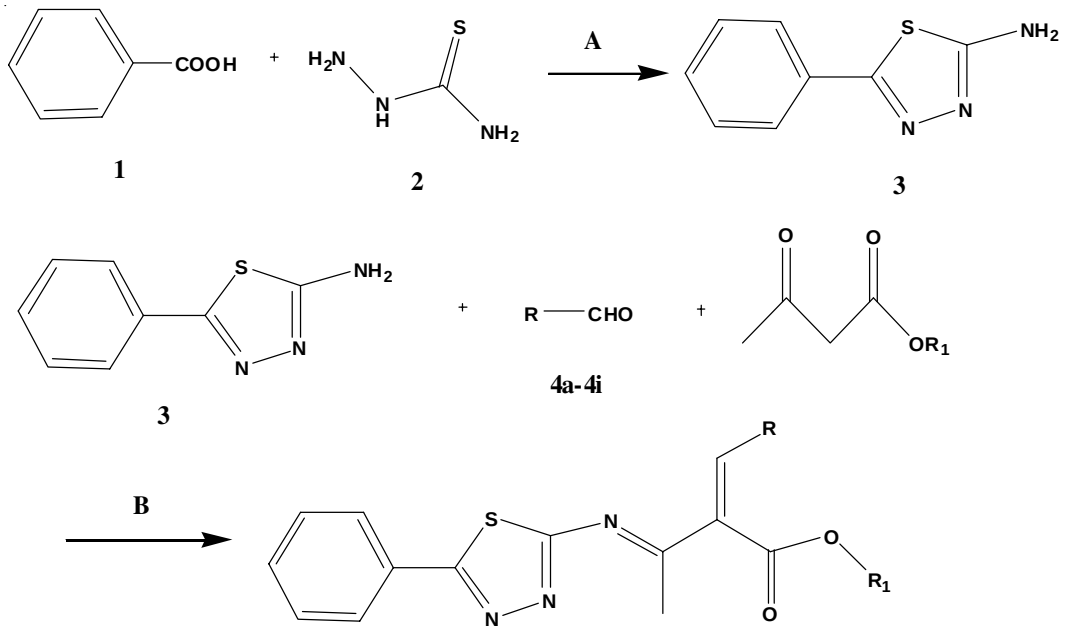

Fig. 1. Synthetic route of schiff bases containing 1,3,4-thiadiazole unit

(5a): In a reaction flask, 0.01 mol of benzaldehye, 0.01 mol of 5-phenyl-1,3,4-thiadiazol-2-amine and 0.012 mol of methyl acetoacetate were dissolved in 200 mL ethanol. Three drops of piperidine and four drops of ice acetic acid were added as catalyst. The mixture was refluxed for 4 h and monitored by TLC. The solvent was removed under reduced pressure, cooled to room temperature and the precipitate was filtered off and recrystallized with ethanol to give a brown crystals. m.p.: 156-157 °C. Yield: 80.2 %. IR (KBr, ν_{max}, cm^{-1}): 3453, 2950.1699, 1582, 1494. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.1 Hz, 2H), 7.51-7.38 (m, 5H), 7.34 (dd, *J* = 15.8, 8.1 Hz, 2H), 7.27 (s, 1H), 6.48 (s, 1H), 3.65 (s, 3H), 2.52 (s, 3H). ESI-MS: *m/z* $[M + H]^+$ 364.2. Anal. Calcd for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56; O, 8.80; S, 8.82. Found C, 66.20; H, 4.81; N, 11.26.

Compounds 5b-i were prepared using the same procedure as 5a

(2Z,3E)-Ethyl-3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)-2-benzylidenebutanoate (5b): Brown crystals, m.p.: 161-163 °C. Yield: 80.9 %; IR (KBr, ν_{max}, cm^{-1}): 3359, 2944, 1678, 1601, 1509. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.59 (m, 2H, Ar-H), 7.49-7.39 (m, 5H, Ar-H), 7.38-7.29 (m, 3H, Ar-H), 7.27 (d, *J* = 1.3 Hz, 1H, Ar-H), 6.48 (s, 1H, =CH), 4.10 (dd, *J* = 7.1, 1.4 Hz, 2H, $-CH_2-$), 2.52 (s, 3H, $-CH_3$), 1.18 (t, *J* = 7.1 Hz, 3H-CH_2CH_3). ESI-MS: *m/z* $[M + H]^+$ 378.2. Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13; O, 8.48; S, 8.49. Found C, 66.92; H, 5.14; N, 11.02; S, 8.39.

(2Z,3E)-Methyl 2-(4-chlorobenzylidene)-3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)butanoate (5c): Brown crystals, m.p.: 161-163 °C. Yield 85.3 %; IR (KBr, ν_{max}, cm^{-1}): 3452, 2975, 1698, 1588, 1498. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.52-7.29 (m, 7H, Ar-H), 6.46 (s, 1H, =CH), 3.66 (s, 3H, $-OCH_3$), 2.52 (s, 3H,$-CH_3$). ESI-MS: *m/z* $[M + H]^+$ 398.3. Anal. Calcd for $C_{20}H_{16}N_3O_2SCl$, C, 60.37; H, 4.05; Cl, 8.91; N, 10.56; S, 8.06. Found C, 60.38; H, 4.13; Cl, 8.83; N, 10.49; S, 8.19

(2Z,3E)-Ethyl 2-(4-chlorobenzylidene)-3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)butanoate (5d): Brown crystals, m.p.: 143-146 °C. Yield: 85.3 %, IR (KBr, ν_{max}, cm^{-1}): 3452, 2945, 1697, 1589,1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.55-7.29 (m, 7H, Ar-H), 6.47 (s, 1H, =CH), 4.11 (q, *J* = 7.2 Hz, 2H-OCH_2-), 2.53 (s, 3H, $-CH_3$), 1.20 (t, *J* = 7.1 Hz, 3H-CH_2CH_3). ESI-MS: *m/z* $[M + H]^+$ 412.2. Anal. Calcd for $C_{21}H_{18}N_3O_2SCl$, C, 61.23; H, 4.40; Cl, 8.61; N, 10.20; S, 7.78. Found C, 61.34; H, 4.47; N, 10.10; S, 7.58.

(2Z,3E)-methyl 3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)-2-((thiophen-2-yl)methylene)butanoate (5e): Brown crystals, m.p. 166-167 °C. Yield: 79.6 %. IR (KBr, ν_{max}, cm^{-1}): 3452, 2942, 1684, 1588, 1506. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.55-7.35 (m, 3H, Ar-H), 7.25 (d, *J* = 5.0 Hz, 1H, Ar-H), 7.06 (d, *J* = 3.5 Hz, 1H, Ar-H), 6.97-6.87 (m, 1H, Ar-H), 6.77 (s, 1H, =CH), 3.72 (s, 3H, $-OCH_3$), 2.52 (s, 3H, $-CH_3$). ESI-MS: *m/z* $[M + H]^+$ 370.2. Anal. Calcd for $C_{18}H_{15}N_3O_2S_2$, C, 58.52; H, 4.09; N, 11.37; S, 17.36. Found C, 58.42; H, 4.20; N, 11.39; S, 17.27.

(2Z,3E)-Ethyl 3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)-2-((thiophen-2-yl)methylene)butanoate (5f): Brown crystals, m.p. 155-156 °C. Yield: 78.2 %. IR (KBr, ν_{max}, cm^{-1}): 3360, 2949, 1680, 1602, 1509. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.70 (m, 2H, Ar-H), 7.49-7.46 (m, 3H, A, r-H), 7.26-6.93 (m, 3H, Ar-H), 6.78 (s, 1H, =CH), 4.19-4.15 (m, 2H, $-CH_2-$), 2.52 (s, 3H, $-CH_3$), 1.25-1.21 (t, 3H, $-CH_3$). ESI-MS: *m/z* $[M + H]^+$ 384.2. Anal. Calcd for $C_{19}H_{17}N_3O_2S_2$, C, 59.51; H, 4.47; N, 10.96; S, 16.72. Found C, 59.49; H, 4.39; N, 10.78; S, 16.30.

(2Z,3E)-Methyl 2-(2-methoxybenzylidene)-3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)butanoate (5g): Brown

crystals, m.p.: 160-162 °C; yield: 70.7 %. IR (KBr, ν_{max}, cm^{-1}): 3452, 2945, 1697, 1589, 1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.9 Hz, 2H. Ar-H), 7.42 (dd, *J* = 14.9, 7.5 Hz, 4H, Ar-H), 7.25 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.93 (dd, *J* = 15.1, 7.5 Hz, 2H, Ar-H), 6.80 (s, 1H, =CH), 3.89 (s, 3H, -OCH_3), 3.63 (s, 3H, CH_3O-Ph), 2.47 (s, 3H, -CH_3). ESI-MS: *m/z* $[M + H]^+$ 394.3. Anal. Calcd for $C_{21}H_{19}N_3O_3S$ C, 64.10; H, 4.87; N, 10.68; S, 8.15 Found C, 64.29; H, 4.73; N, 10.47; S, 8.27.

(2Z,3E)-Ethyl 2-(2-methoxybenzylidene)-3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)butanoate (5h): Brown crystals, m.p.: 168-170 °C; yield: 72.6 %. IR (KBr, ν_{max}, cm^{-1}): 3428, 2986, 1671, 1582, 1499. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.7 Hz, 2H, Ar-H), 7.48-7.34 (m, 4H, Ar-H), 7.24 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.92 (dd, *J* = 17.4, 8.0 Hz, 2H, Ar-H), 6.82 (s, 1H, =CH), 4.07 (q, *J* = 7.1 Hz, 2H, -CH_2-CH_3), 3.89 (s, 3H, -OCH_3), 2.48 (s, 3H, -CH_3), 1.18 (t, *J* = 7.1 Hz, 3H, CH_3-CH_2-). ESI-MS: *m/z* $[M + H]^+$ 408.3. Anal. Calcd for $C_{22}H_{21}N_3O_3S$, C, 64.85; H, 5.19; N, 10.31; S, 7.87 Found C, 64.78; H, 5.26; N, 10.28; S, 7.79.

(2Z,3E)-Ethyl 2-(4-bromobenzylidene)-3-(5-phenyl-1,3,4-thiadiazol-2-ylimino)butanoate (5i): Brown crystals, m.p.: 151-152 °C; yield: 82.7 %. IR (KBr, ν_{max}, cm^{-1}): 3376, 2947, 1685, 1599, 1503. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.52-7.40 (m, 5H, Ar-H), 7.33 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.45 (s, 1H, Ar-H), 4.11 (q, *J* = 7.1 Hz, 2H-CH_2CH_3), 2.51 (s, 3H, -CH_3), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3-CH_2-). ESI-MS: *m/z* $[M + H]^+$ 455.2. Anal. Calcd for $C_{21}H_{18}BrN_3O_2S$ C, 55.27; H, 3.98; Br, 17.51; N, 9.21; S, 7.03. Found C, 55.36; H, 3.78; Br, 17.46; N, 9.32; S, 7.09.

RESULTS AND DISCUSSION

We have developed a convenient, simplified and efficient approach to synthesize Schiff bases *via* three component condensation reaction. Compared with the reported synthesis, only two steps were required to obtain the aimed product conveniently in high yield, as shown in Table-1.

We attempted to speculate the mechanism of the reaction based on experimental facts. It is found that compound B was

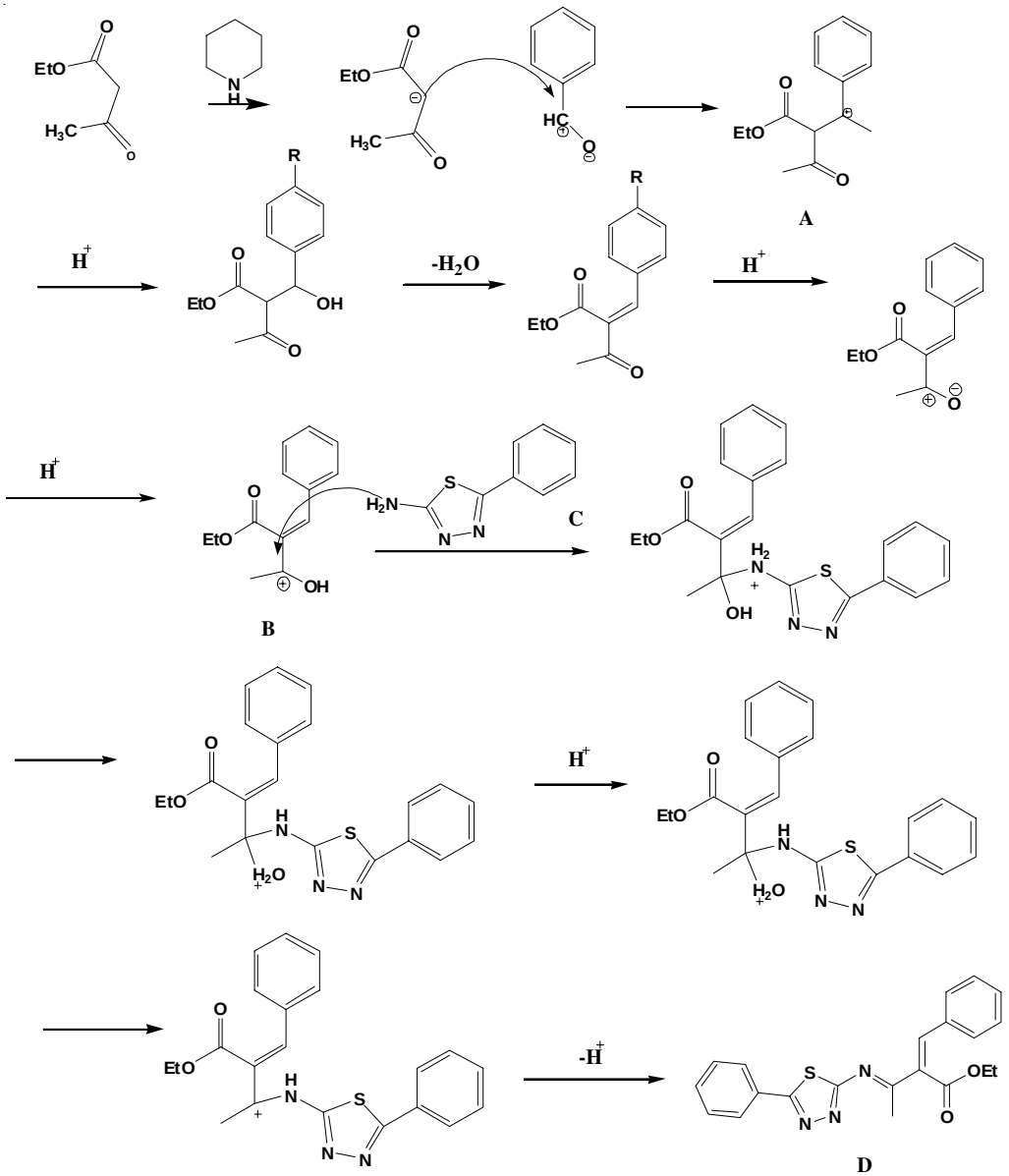

Fig. 2. A possible mechanisms for the synthesis **5a-i** (the synthesis of **5a** taken as an example)

TABLE-1
SUBSTITUTION OF COMPOUND AND SYNTHESIS OF **5a-i**

Compound	R	R1	Time (h)	Yield (%)	
				(One pot)	(Multistep)
5a	Benzaldehyde	Me	4	80.2	40.6
5b	Benzaldehyde	Et	4	80.9	42.7
5c	*p*-Chlorobenzaldehyde	Me	4	85.3	45.5
5d	*p*-Chlorobenzaldehyde	Et	4	86.3	47.3
5e	2-Thenaldehyde	Me	4	79.6	39.7
5f	2-Thenaldehyde	Et	4	78.2	36.6
5g	*o*-Anisaldehyde	Me	4	70.7	32.5
5h	*o*-Anisaldehyde	Et	4	72.6	35.5
5i	4-Bromobenzaldehyde	Et	4	80.7	39.8

obtained when piperidine was added solely and compound D was obtained when a few drops of acetic acid was added. Furthermore, I_2 is required for this reaction, compared with the absence of I_2, the aimed product would be obtained in high yield when I_2 was added, so a possible mechanism was proposed (Fig. 2).

First, compound A was formed *via* Knoevenagel reaction of methyl acetoacetate with aromatic aldehyde took place in the presence of piperidine and then A was transformed to B The carbonyl was activated by the addition of acetic acid, so it is easy for compound C to attack B and formed compound D.

Conclusion

A novel, simple and efficient procedure for the preparation of novel Schiff bases was demonstrated *via* a three component condensation reaction of aromatic aldehyde, methyl or ethyl acetoacetate and 5-phenyl-1,3,4-thiadiazol-2-amine, in refluxing-ethanol. A variety of chosen common substrates participated in the process with operational simplicity, excellent yields, short reaction time and environmentally friendly.

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