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Short Communication

Synthesis and Spectroscopic Studies of New Schiff Bases

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Abstract: Five novel Schiff bases have been prepared from *o*-formylphenoxyacetic acid and a series of aminothiazoles to form a number of potentially biologically active compounds. The structures of these Schiff bases have been characterized using IR and ^{1}H- and ^{13}C-NMR spectroscopy.

Keywords: aminothiazoles, *o*-formylphenoxyacetic acid, Schiff bases, biological activity

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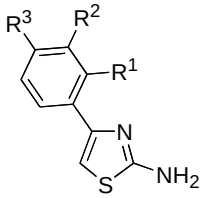
Introduction

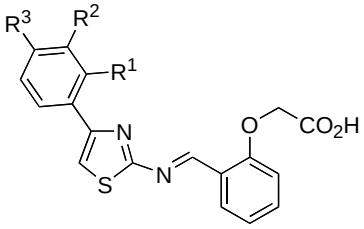
Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition, and replacement reactions [1]. Moreover, Schiff bases are also known to have biological activities such as antimicrobial [2-5], antifungal [4-6], antitumor [7-9], and as herbicides [10]. Schiff bases have also been employed as ligands for complexation of metal ions [11]. On the industrial scale, they have wide range of applications such as dyes and pigments [12]. Keeping in view the facts mentioned, we decided to synthesize new Schiff bases which were predicted to have useful biological activity. The synthesis of other similar Schiff bases, their biological activity, and complex formation are under study.

Results and Discussion

The Schiff bases **2a-e** were synthesized by condensation of *o*-formylphenoxyacetic acid and aryl aminothiazoles **1a-e** by reaction in hot ethanol or dioxane using sodium sulfate as a dehydrating agent. The aminothiazoles were prepared by the known [13] reaction of thiourea with substituted acetophenones in the presence of iodine as oxidant. Good yields were obtained for the Schiff bases, although in some cases the addition of ytterbium triflate was found to improve the yield of product, it acting as a Lewis acid catalyst.



1a-e



2a-e

a R^1 = Br, R^2 = H, R^3 = H
b R^1 = H, R^2 = H, R^3 = Br
c R^1 = F, R^2 = H, R^3 = H
d R^1 = H, R^2 = F, R^3 = H
e R^1 = H, R^2 = H, R^3 = F

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Experimental

General

Bromoacetophenones, chloroacetophenones and fluoroacetophenones were obtained commercially from Lancaster Research Chemicals and 2-formylphenoxyactic acid from the Aldrich Chemical Company. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX-400 instrument at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm referenced to the residual solvent signal. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. Mass spectra were recorded on a Jeol SX-102 instrument using FAB ionization. Melting points were recorded on a Stuart Scientific-SMP3 apparatus and are uncorrected.

Synthesis of 2-amino-4-(2'-bromophenyl)-thiazole (**1a**)

Method A: The title compound was prepared by addition of resublimed iodine (2.54 g, 0.01 mol) to 2'-bromoacetophenone (1.99 g, 0.01 mol) and thiourea (1.52 g, 0.02 mol), followed by heating of the mixture overnight in an oil bath at 100 °C. After cooling, the reaction mixture was triturated with diethyl ether (*ca*. 50 mL) to remove any unreacted iodine and bromoacetophenone. The solid residue was put in cold distilled water (200 mL) and treated with 25% aqueous ammonium hydroxide (to pH 9-10). The precipitated thiazole was collected and purified by crystallization from hot ethanol. The yield was 85% and m.p. 123 °C; FABMS: *m/z* 255 (MH^+) , in agreement with the molecular formula

$C_9H_7BrN_2S$; IR; IR (υ_{max}, KBr, cm^{-1}): 3320 (d of NH_2); 1510, 1460, 1045 (characteristic of the thiazole nucleus); ^{1}H-NMR (MeOH-d_4): δ 6.87 (1H, s, thiazole H-5), 7.34 (1H, td, *J* 11.6, 1.6 Hz, ArH), 7.45 (1H, td. *J* 7.6,1.6 Hz, ArH), 7.58 (1H, dd, *J* 7.2, 1.2 Hz, ArH), 7.72 (1H, dd, *J* 8.0,1.2 Hz, ArH); ^{13}C-NMR (MeOH-d_4): δ 171.2, 144.6, 134.9, 133.1, 131.7, 130.0, 128.8, 123.4, 107.7; Anal. Calcd. for $C_9H_7BrN_2S$: C, 42.37; H, 2.77; N, 10.98; Found: C, 42.39; H, 2.76; N, 10.96.

Method B: 2-Amino-4-(2'-bromophenyl)-thiazole was also prepared following the reported procedure [14]. The spectroscopic data of the compound **1a** thus prepared were identical to those given above.

The following compounds were prepared by *Method A*, as described above:

2-amino-4-(4'-bromophenyl)thiazole (**1b**)

Yield: 80%; m.p. 178 ºC; FABMS: *m/z* 255 (MH^+), in agreement with the molecular formula $C_9H_7BrN_2S$; IR (υ_{max}, KBr, cm^{-1}): 3320 (d of NH_2); 1515, 1455, 1050 (characteristic of the thiazole nucleus); ^{1}H-NMR (DMSO-d_6): δ 8.7-7.8 (2H, bs, NH_2), 7.67 (4H, s, ArH), 7.07 (1H, s, thiazole H-5); ^{13}C-NMR (DMSO-d_6): δ 169.7, 140.7, 131.8, 129.5, 127.8, 122.0, 103.5; Anal. Calcd. for $C_9H_7BrN_2S$: C, 42.37; H, 2.77; N, 10.98; Found: C, 42.35; H, 2.75; N, 10.97.

2-amino-4-(2'-fluorophenyl)thiazole (**1c**)

Yield: 97%; FABMS: *m/z* 195 (MH^+), in agreement with the molecular formula $C_9H_7FN_2S$; IR (υ_{max}, KBr, cm^{-1}): 3320 (d of NH_2); 1510, 1455, 1050 (characteristic of the thiazole nucleus); ^{1}H-NMR (MeOH-d_4): δ 6.93 (1H, s, thiazole H-5), 7.13-7.36 (3H, m, ArH), 7.93 (1H, td, *J* 7.9, 1.7 Hz, ArH); ^{13}C-NMR (MeOH-d_4): δ 170.7, 145.1, 133.5, 133.4, 132.4, 131.4, 130.8, 128.2 and 107.9. Anal. Calcd. for $C_9H_7FN_2S$: C, 55.66; H, 3.63; N, 14.42; Found: C, 55.62; H, 3.59; N, 14.41.

2-amino-4-(3'-fluorophenyl)thiazole (**1d**)

Yield: 86%; FABMS: *m/z* 194 (MH^+), in agreement with the molecular formula $C_9H_7FN_2S$; IR (υ_{max}, KBr, cm^{-1}): 3320 (d of NH_2); 1510, 1460, 1045 (characteristic of the thiazole nucleus); ^{1}H-NMR (MeOH-d_4): δ 7.01 (s, thiazole H-5), 7.09-7.56 (4H, m, ArH); ^{13}C-NMR (MeOH-d_4): δ 171.8, 165.7, 163.3, 135.9, 131.7, 122.8, 116.2, 113.8 and 104.5. Anal. Calcd. for $C_9H_7FN_2S$: C,55.66; H, 3.63, N, 14.42; Found: C, 55.60; H, 3.58, N, 14.39.

2-amino-4-(4'-fluorophenyl)thiazole (**1e**)

Yield: 87%; FABMS: *m/z* 195 (MH^+), in agreement with the molecular formula $C_9H_7FN_2S$; IR (υ_{max}, KBr, cm^{-1}): 3320 (d of NH_2); 1510, 1460,1045 (characteristic of the thiazole nucleus); ^{1}H-NMR (Py-d_5): δ 7.31 (2H, brs, NH_2), 8.10 (1H, s, thiazole H-5), 8.18-9.20 (4H, m, ArH); ^{13}C (Py-d_5): δ 171.4, 165.2, 162.7, 133.9, 129.9, 129.8, 117.3, 117.1 and 103.5; Anal. Calcd. for $C_9H_7N_2FS$: C, 55.66; H, 3.63; N, 14.42; Found: C, 55.65; H, 3.61; N, 14.40.

Preparation of (2-{[4-(2-bromophenyl)thiazol-2-ylimino]methyl}phenoxy)acetic acid (**2a**):

2-Formylphenoxyacetic acid (4.0 mmol, 0.72 g) was added to 2-amino-4-(2'-bromophenyl)-thiazole (4.0 mmol, 1.02 g) in absolute EtOH (20 mL) in addition to molecular sieves (4Å, *ca*. 5 g) and Na_2SO_4 (anhydr. *ca*. 5 g) and refluxed (oil bath at 90 ºC) for 3 days under N_2 (g). After filtration, evaporation and recrystallisation from EtOH the yield of the title Schiff base was found to be 60%; m.p. 180 ºC; HRMS (FAB, MH^+) calcd. for $C_{18}H_{13}N_2O_3BrS$: 416.9909, found: 416.9904; IR (υ_{max}, KBr, cm^{-1}): 3030, 1635, 1550, 1240 cm^{-1}; ^{1}H-NMR, (MeOH-d_4): δ 5.77 (2H, s, CH_2), 6.91 (1H, d, *J* 9.2 Hz, ArH), 7.46-7.73 (7H, m, ArH), 7.92 (1H, s CH=N); ^{13}C-NMR (MeOH-d_4): δ 67.1, 113.4, 122.1, 122.3, 128.4, 129.5, 130.0, 130.8, 131.1, 130.3, 133.2, 133.8, 136.4, 144.9, 156.3, 1661.5,168.9, 172.0; Anal. Calcd. for $C_{18}H_{13}BrN_2O_3S$: C, 51.81; H, 3.14; N, 6.71. Found: C, 51.79, H, 3.12; N, 6.69;

Preparation of (2-{[4-(4-bromophenyl)-thiazole-2-ylimino]methyl}phenoxy)acetic acid (**2b**)

2-Formylphenoxyacetic acid (4.0 mmol, 0.72 g) was added to a solution of 2-amino-4-(4'-bromophenyl)-thiazole (4.0 mmol, 1.02 g) in dioxane (40 mL) in addition to molecular sieves (4Å, *ca*. 5 g) and Na_2SO_4 (anhydr. *ca*. 5 g) and refluxed above 100 ºC for 2 days under N_2 (g). The product was purified by crystallization from EtOH and the yield of the Schiff base was found to be 67%; m.p. 185-187 ºC; HRMS (FAB, MH^+) calcd. for $C_{18}H_{13}BrO_3N_2S$: 416.9909, found: 416.9904; IR (υ_{max}, KBr, cm^{-1}): 3030, 1650, 1550, 1240. Anal. Calcd. for $C_{18}H_{13}BrO_3N_2S$: C, 51.81; H, 3.14; N, 6.71. Found: C, 51.80, H, 3.10; N, 6.70; ^{1}H-NMR, (MeOH-d_4): δ 6.17 (2H, s, CH_2), 6.77 (1H, d, J 8.0 Hz, ArH) 7.10-7.63 (7H, m, ArH), 7.99 (1H, s, CH=N); ^{13}C-NMR (MeOH-d_4): δ 65.9,113.4, 122.8, 122.9, 123.9, 124.4, 129.4, 129.8, 130.7, 131.0, 131.1, 131.2, 132.8, 132.9, 140.1, 156.3, 160.9, 172.0

Preparation of (2-{[4-(2'-fluorophenyl)-thiazole-2-ylimino]methyl}phenoxy)acetic acid (**2c**)

2-Formylphenoxyacetic acid (1.0 mmol, 0.18 g) was added to a solution of 2-amino-4-(2'-fluorophenyl)-thiazole (1.0 mmol, 0.19 g) in absolute EtOH (10 mL) in addition to 10% mmol of $Yb(OTf)_3$ as Lewis catalyst and refluxed for 10 hours under N_2 (g). The reaction mixture was filtered through a column of silica gel, charcoal and Celite® to remove the catalyst. After evaporation of the ethanol, the product was purified by recrystallisation from $CHCl_3$/MeOH (a few drops) to give the Schiff base in 70% yield; m.p. 167 ºC; HRMS (FAB, MH^+) calcd. for $C_{18}H_{13}FN_2O_3S$: 357.0709, found: 357.0712; IR (υ_{max}, KBr, cm^{-1}): 3030, 1640, 1550, 1240; ^{1}H-NMR, (MeOH-d_4): δ 5.64 (2H, s, CH_2), 6.79-7.68 (8H, m, ArH), 7.99 (1H, s, CH=N); ^{13}C-NMR (MeOH-d_4): δ 66.3, 116.8, 122.2, 122.5, 125.1, 126.3, 128.1, 128.4, 129.3, 130.3, 130.9, 132.9, 138.2, 140.1, 157.2, 160.1, 169.5, 172.8; Anal. calcd. for $C_{18}H_{13}FN_2O_3S$: C, 51.81; H, 3.14; N, 6.71. Found: C, 51.60, H, 3.08; N, 6.64;

Preparation of (2-{[4-(3'-fluorophenyl)thiazole-2-ylimino]methyl}phenoxy)acetic acid (**2d**)

Compound **2d** was synthesized by the method described above. The product was purified by crystallization from chloroform and the yield of the title Schiff base was 70%; m.p. 178 ºC (decomp.); HRMS (FAB, MH^+) calcd. for $C_{18}H_{13}FN_2O_3S$: 357.0709; found: 357.0712; IR (υ_{max}, KBr, cm^{-1}): 3030, 1635, 1550, 1240; ^{1}H-NMR (MeOH-d_4): δ 6.15 (2H, s, CH_2), 6.93-7.37 (8H, m, ArH), 7.91 (1H, s,

CH=N); ^{13}C-NMR (MeOH-d_4): δ 66.3, 113.4, 116.4, 122.3, 124.6, 124.9, 125.3, 129.4, 130.4, 131.2, 131.3, 131.5, 131.6, 138.9, 140.9, 157.9, 162.4, 169.7; Anal. Calcd. for $C_{18}H_{13}FN_2O_3S$: C, 51.81; H, 3.14; N, 6.71. Found: C, 51.64, H, 3.10; N, 6.56.

Preparation of (2-{[4-(4'-fluorophenyl)-thiazole-2-ylimino]methyl}phenoxy)acetic acid (**2e**)

Compound **2e** was synthesized by the method described above. The product was purified by crystallization from chloroform and the yield of the Schiff base was 70%; m.p. 158-160 ºC; HRMS (FAB, MH^+) calcd. for $C_{18}H_{13}FN_2O_3S$: 357.0709, found: 357.0713; IR (υ_{max}, KBr, cm^{-1}): 3030, 1630, 1550, 1240; ^{1}H-NMR (MeOH-d_4): δ 6.09 (2H, s, CH_2), 6.90-7.48 (8H, m, ArH), 7.91 (1H, s, CH=N); ^{13}C-NMR (MeOH-d_4): δ 66.0,113.4, 116.6, 116.8, 122.9, 123.6, 128.0, 129.4, 130.5, 131.0, 131.7, 131.8, 138.9, 140.6, 156.4,163.2, 165.7, 171.6; Anal. Calcd. for $C_{18}H_{13}FN_2O_3S$: C, 51.81; H, 3.14; N, 6.71. Found: C, 51.59, H, 3.40; N, 6.49;

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Sample availability: Contact the authors