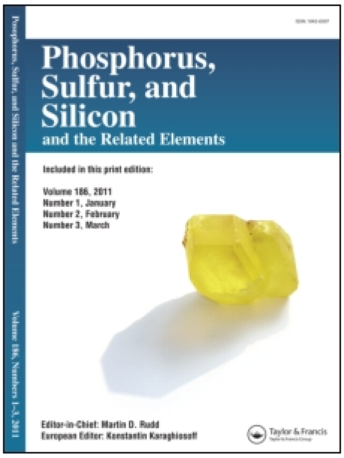

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Synthesis and Chemical Behavior of 2-Chloro -3-(2"-Thienoylmethyl) Quinoxaline Towards Some Nucleophilic Reagents

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SYNTHESIS AND CHEMICAL BEHAVIOR OF 2-CHLORO -3-(2′-THIENOYLMETHYL) QUINOXALINE TOWARDS SOME NUCLEOPHILIC REAGENTS

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2-Chloro-3-(2′-thenoylmethyl)quinoxaline (3) was prepared by the reaction of *o*-phenylenediamine and 2-thenoylpyruvate, followed by the treatment with phosphorus oxychloride. The chemical behavior of 3 towards nucleophilic reagents (such as amines, acid hydrazides, alkoxides and sodium hydroxide) is described.

Keywords: Nucleophilic reagents; quinoxalines

Quinoxaline derivatives exhibit antifungal[1–2] and antidepresent activities.[3] The aim of the present work was to study the chemical behavior of 2-chloro-3-(2′-thienoylmethyl)quinoxaline (3) towards some nucleophilic reagents (such as amines, acid hydrazides, alkoxides and sodium hydroxide) to produce new quinoxaline compounds expected to exhibit biological activity.[4,5]

The 2-thenoylpyruvate (1) was prepared 2-acetylthiophene and diethyl oxalate in the presence of sodium methoxide according to a literature method.[6] The 2-chloro-3-(2′-thienoylmethyl)quinoxaline (3) was obtained by the reaction of *o*-phenylenediamine and 2-thienoylpyruvate (1) in 4*N* hydrochloric acid to give 2-hydroxy-3-(2′thenoylmethyl)quinoxaline (2), followed by the treatment of 2 with phosphorus oxychloride (Scheme 1).[3]

Treatment of 2-chloro-3-(2′-thenoylmethyl)quinoxaline (3) with amities (such as *p*-toluidine and hydroxylamine hydrochloride) in the presence of

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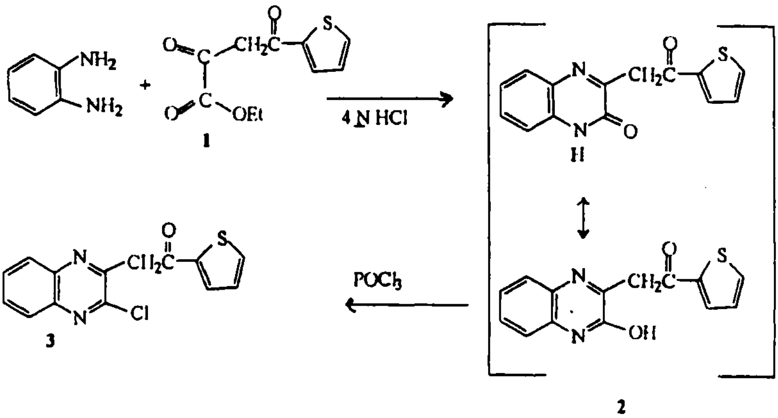
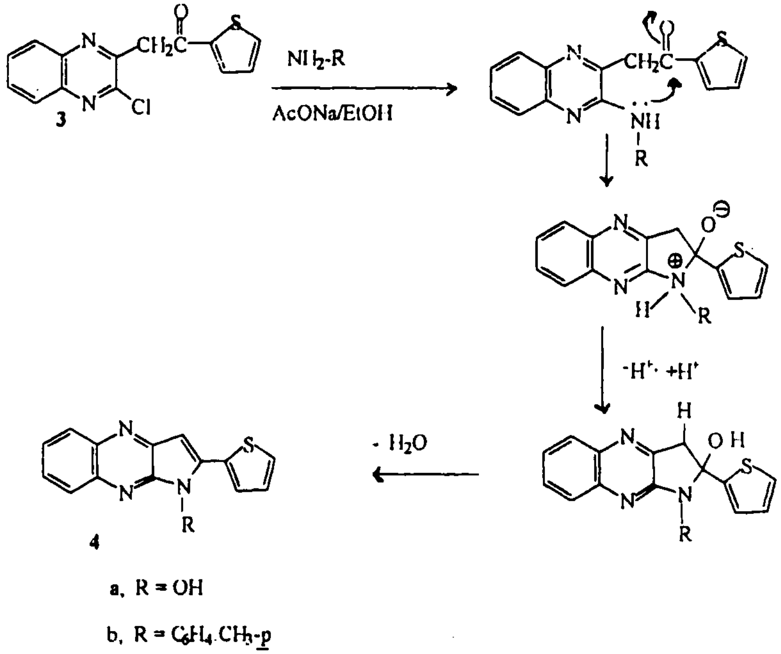
* Correspondence Author



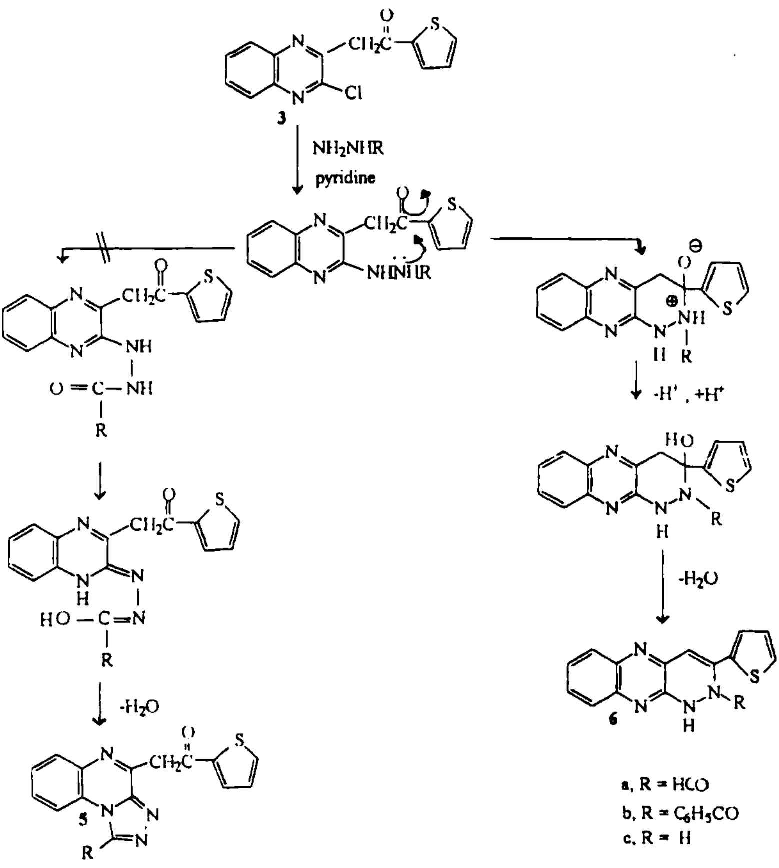
SCHEME 1

fused sodium acetate in ethanol led to the formation of 1-substituted-2-thienylpyrolo[2,3-b]quinoxaline (4, Scheme 2).



SCHEME 2

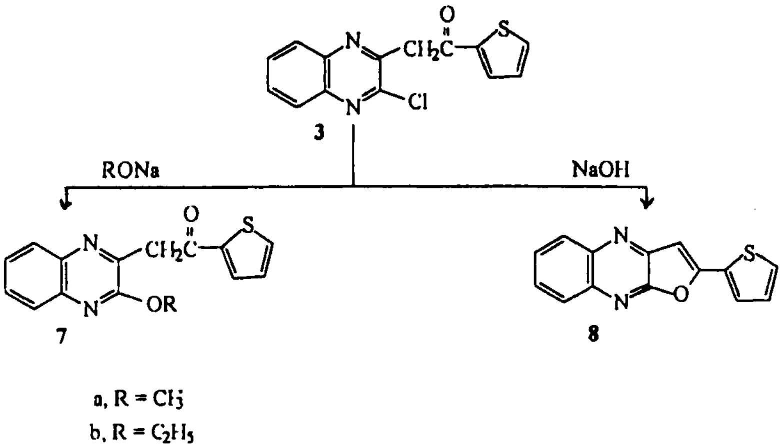
In the present investigation it was expected that the reaction of 2-chloro-3-(2′-thenoylmethyl)quinoxaline (**3**) with acid hydrazides (such as formoylhydrazine and benzoylhydrazine) in pyridine under reflux for 15 h would produce triazoloquinoxaline **5** reported in literature.[7] However, the new product proved to be 2′-substituted-3-thienylpyridazino[2,3-*b*]quinoxaline (6a-b, Scheme 3). Subsequently, compound **3** was allowed to react with hydrazine hydrate in pyridine to give the corresponding 3-thienylpyridazino[2,3-*b*]quinoxaline (7c, Scheme 3).



SCHEME 3

The 2-chloro-3-(2′-thenoylmethyl)quinoxaline (3) treated with alkoxides (such as methoxide and ethoxide) under reflux for 4 h afforded the corresponding 2-alkoxy-3-(2′-thenoylmethyl)quinixaline (7a,b; Scheme 4).

In present detailed work the reaction of 3 with aqueous sodium hydroxide (1 mol/L) led to the formation of 2-thienylfuro[2,3-*b*]quinoxaline (8, Scheme 4).



SCHEME 4

EXPERIMENTAL

Melting points were determined in capillaries with a Thomas-Hover Uni-Melt apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer using KBr wafers. Proton NMR spectra were obtained on a Varian Em 360 spectrometer using solutions in hexadeuteriodimethyl sulfoxide with tetramethylsilane as the internal standard. Mass spectra were taken on a VG 12–250 instrument (70 eV EI ionzation, source temperature 200 °C).

3-Thienoylmethyl-2- quinoxaltionone (2)

A mixture of *o*-phenylenediamine (0.01 mol) and 2-thienoylpyruvate (0.01 mol) was heated under reflux with stirring in 4 *N* hydrochloric acid

(60 mL) for 3 h. The solid formed was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 2 as colourless crystals, yield 82%, mp: 281 – 282°C. ν_{max}(KBr): 3205 (NH), 1707, 1680 (C=O), 1635 (C=N) cm^{-1}. δ_H ($DCCl_3$): 2.56 (s, 2 H, CH_2CO), 7.26(s, 1H, C-4, thiophene ring), 7.8–7.84 (s, 2H, C-3; 5, thiophene ring), 7.64–7.68 (t, 2 H, Ar-H), 7.86 – 7.89 (δ, 2 H, Ar-H) and 11.59 (s, 1 H, NH) ppm. MS: m/z = 270 (M^+) Anal. $C_{14}H_{10}N_2O_2S$ Calcd for : C, 62.22; H, 3.70; N, 10.37, S, 11.85. Found : C, 62.01 H, 3.51; N, 10.23; S, 11.64.

2-Chloro-3-(2′-thienoylmethyl)quinoxaline (3)

A solution of **2** (0.01 mol) in phosphorus oxychloride (30 mL) was heated on a water-bath under reflux for 5 h. The mixture was cooled, poured onto crushed ice. The product formed was collected by filtration, washed with ice-water, dried and crystallized from ethanol to give 3 as pale yellow crystals, yield 71%, mp: 143–144 °C. ν_{max} (KBr): 1705 (C=O), 1630 (C=N) cm^{-1}. δ_H ($DCCl_3$): 2.52(s, 2H, CH_2CO), 7.23 (s, 1H, C-4, thiophene ring), 7.81 – 7.83 (s, 2H, C - 3,5, thiophene ring), 7.62–7.67 (t, 2 H, Ar-H), 7.85–7.88 (d, 2 H, Ar-H) ppm. Ms: m/z = 290.5 (M^++2), 289.5 (M^++1), 288.5 (M^+). Anal. $C_{14}H_9ClN_2OS$ for Calcd: C, 58.23; H, 3.12; N, 9.71; Cl, 12.30; S, 11.09. Found: C, 58.01; H, 2.98; N, 9.56; Cl, 12.07; S, 10.85.

1-Substituted 2-thienylpyrolo [2,3-*b*]quinoxaline (4)

A mixture of **3** (0.01 mol), amines (namely, hydroxylamine hydrochloride and *p*-toluidine) (0.01 mol) and sodium acetate (0.02 mol) in ethanol was heated under reflux for 24 h, then cooled and poured into water. The solid obtained was filtered off, washed with water, dried and purified by recrystullization with ethanol to give 4.

Compound **4a** as pale yellow crystals, yield 61%, mp: 245–246 °C. ν_{max} (KBr) : 3510 (OH), 1635, 1600, 1570 cm^{-1}. δ_H(DMSO-d_6) 6.21 (s, 1H, C-3, pyrrole ring), 7.21 (s, 1H, C-4, thiophene ring), 7.80–7.82 (s, 2 H, C-3, 5, thiophene ring) 7.62–7.66 (t, 2 H, Ar-H), 7.84–7.87 (d, 2 H, Ar-H) and 11.10 (s, 1 H, OH) ppm. MS: m/z = 269 (M^++2), 268 (M^++1), 267 (M^+). Anal. $C_{14}H_9N_3OS$ for Calcd : C,62.92; H, 3.37; N, 15.73; S, 11.98. Found: C, 62.90; H, 3.34; N, 15.67; S, 11.73.

Compound **4b** as yellow crystals, yield 67%, mp: 254 °C. ν_{max} (KBr): 1635, 1610, 1600, 1575 cm^{-1}. δ_H(DMSO-d_6): 2.3 (s, 3H, CH_3), 6.20 (s, 1H, C-3, pyrrole ring), 7.22 (s, 1 H, C-4, thiophene ring), 7.80–7.82 (s, 2 H, C-3, 5, thiophene ring), 7.62–7.68 (t, 2 H, Ar-H), 7.84–7.87 (d, 2 H, Ar-H) ppm. MS: m/z = 341(M^+), 340 (M^+-1), 339 (M^+-2). Anal. $C_{21}H_{15}N_3S$ for Cacld : C, 73.90; H, 4.40; N, 12.32; S, 9.38. Found: C, 73.70; H, 4.17; N, 12.03; S, 9.07.

2-Substituted 3-Thienylpyridazino[2, 3-*b*] quinoxaline (6a-c)

A solution of **3** (0.01 mol) and hydrazine derivatives (namely, formoyl hydrazine, benzoylhydrazine and hydrazine hydrate) (0.01 mol) in pyridine (50 mL) was heated under reflux for 16 h, and then cooled and acidified with dilute hydrochloric acid (2%). The deposited solid was filtered, washed with water, dried and recrystallized from ethanol to give **6**.

Compound **6a** as yellow crystals, yield 64%, mp: 271 °C. ν_{max}(KBr): 3215 (NH), 1697(C=O), 1632, 1610, 1580 cm^{-1}. δ_H (DMSO-d_6): 7.21 (s, 1H, C-4, thiophene ring), 7.81–7.83 (s, 2H, C-3, 5, thiopene ring), 7.62–7.71 (m, 3H, Ar-H and pyridazine), 7.84–7.86 (d, 2H, Ar-H), 9.6 (s, 1H, CHO) and 11.3 (s, 1H, NH) ppm. MS: m/z = 294 (M^+), 293 (M^+-1). Anal: $C_{15}H_{10}N_4OS$ for Calcd: C, 61.22; H, 3.40; N, 19.05; S, 10.88. Found: C, 61.36; H, 3.26; N, 18.87; S, 10.57.

Compound **6b** as yellow crystals, yield 65%, mp: 281 °C. ν_{max} (KBr): 3220 (NH), 1695 (C= 0), 1635, 1615,1600, 1580 cm^{-1}. δ_H(DMSO-d_6) 7.10–7.91 (m, 13H, Ar-H, thiophene and pyridazine) and 11.50 (s, 1H, NH) ppm. MS: m/z = 370 (M^+), 369 (M^+-1). Anal. $C_{21}H_{14}N_4OS$ for Calcd: C, 68.11; H, 3.52; N, 15.01; S, 8.40. Found: C, 68.00; H, 3.42; N, 14.89; S, 8.23.

Compound **6c** as yellow crystals, yield 63%, mp: 254 °C. ν_{max}(KBr): 3275 (NH), 1635, 1610, 1605, 1580 cm^{-1}. δ_H (DMSO-d_6): 7.20 (s, 1H, C-4, thiophene), 7.80–7.82 (s, 2H, C-3, 5, thiophene), 7.61–7.71 (m, 3H, Ar-H and pyridazine), 7.83–7.86 (d, 2H, Ar-H), 11.30–11.51 (br, s, 2H, NH) ppm. MS: m/z = 266 (M^+), 264 (M^+-2). Anal. $C_{14}H_{10}N_4S$ for Calcd : C, 63.16; H, 3.76; N, 21.05; S, 12.03. Found: C, 63.00; H, 3.48; N, 20.98; S, 12.30.

2-Alkoxy-3-(2′-thienoylmethyl)quinoxaline (7a,b)

A solution of **3** (0.01 mol) and sodium alkoxide (namely, methoxide and ethoxide) in alcohol (30 ml) was heated under reflux for 6 h. The reaction mixture was cooled and acidified with 1 *M* hydrochloric acid. The crude product was isolated by filtration and purified by crystallization from benzene to give **7**.

Compound **7a** as colourless crystals, yield 53%, mp: 89 °C. ν_{max}(KBr): 3067, 1695, 1630, 1611, 1580, 1080 cm^{-1}. δ_H($DCCl_3$): 2.51 (s, 2H, $COCH_2$), 3.71 (s, 3H, OCH_3), 7.21(s, 1H, C-4, thiophene ring), 7.61–7.66 (t, 2H, Ar-H), 7.80–7.82 (s, 2H, C-3, 5, thiophene ring), and 7.86–7.88 (d, 2H, Ar-H) ppm. MS: m/z = 284 (M^+). Anal. $C_{15}H_{12}N_2O_2S$ for Calcd: C, 63.38; H, 4.23; N, 9.86; S, 11.27. Found: C, 63.07; H, 4.03; N, 9.59; S, 10.98.

Compound **7b** as colourless crystals, yield 59%, mp: 83 °C. δ_H($DCCl_3$): 1.20 (t, 3 H, CH_3), 2.54 (s, 2H, $COCH_2$), 3.75 (q, 2H, CH_2O), 7.20 (s, 1H, C-4, thiophene ring), 7.62–7.67 (t, 2 H, Ar-H), 7.81–7.83 (s, 2 H, C-3, 5, thiophene ring) and 7.89- 7.87 (d, 2H, Ar-H) ppm. MS: m/z = 298 (M^+). Anal. $C_{16}H_{14}N_2O_2S$ for Calcd: C, 64.43; H, 4.70; N, 9.40; S, 10.74. Found: C, 64.01; H, 4.48; N, 9.11; S, 10.39.

2-Thienylfuro[2, 3-b]quinoxaline (8)

A solution of **3** (0.01 mol) in dioxane (30mL) was added to a boiling solution of aqueous sodium hydroxide (1 mol/L, 25 ml). The reaction mixture was heated under reflux for 4 h, then cooled and acidified with hydrochloric acid (2 M/L). The deposited solid was filtered off and purified by crystallization with acetic acid to give 8 as pale yellow crystals, yield 52%, mp: 269 °C. ν_{max} (KBr): 3065, 1630, 1601, 1580, 1215, 1050 cm^{-1} δ_H (DMSO-d_6): 6.57 (s, 1H, C-3, furan ring), 7.21 (s, 1H, C-4, thiopren ring), and 7.83–7.88 (t, 2 H, Ar- H), 7.80–7.82 (s, 2 H, C-3, 5, thiophene ring) and 7.83–7.88 (d, 2H, Ar-H) ppm. MS: M/z = 252 (M^+). Anal. $C_{14}H_8N_2OS$ for Calcd: C, 66.66; H, 3.17; N, 11.11; S, 12.70. Found: C, 66.36; H, 2.97; N, 10.98; S, 12.53.

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