One-pot, procedure for the preparation of some thiazino[2,3-b]quinoxaline derivatives

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An efficient and convenient synthesis of new thiazino[2,3-b]quinoxaline derivatives has been developed by employing a one-pot cyclo-condensation of several α-haloketones and 3-aminoquinoxaline-2-thiol in acetic acid. A similar reaction with 4-bromo-3-methyl-4,5-dihydro-1H-5-pyrazolone gave a new heterocyclic system, 3-methyl-1,4-dihydropyrazolo[4',3':5,6][1,4] thiazino[2,3-b]quinoxaline.

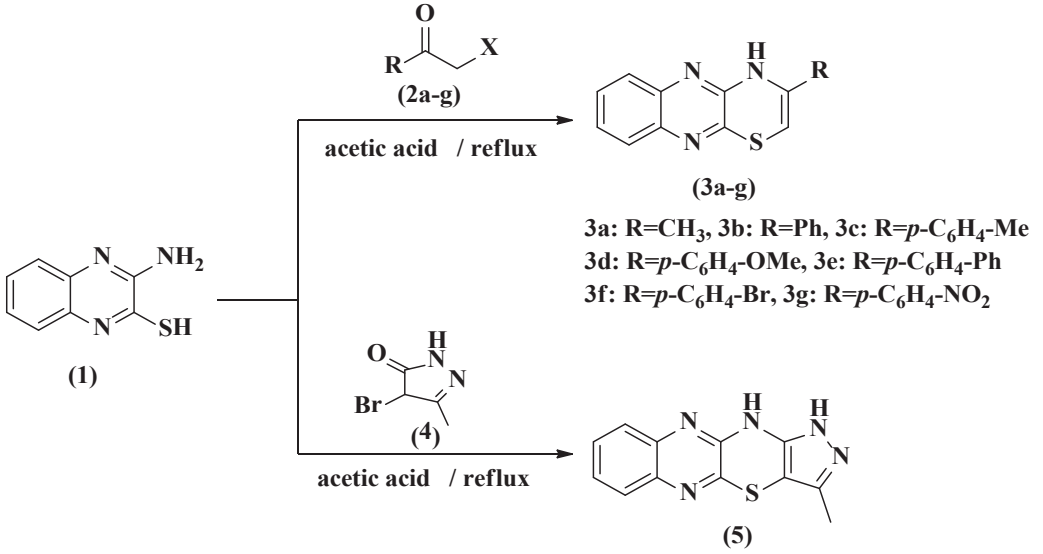
Keywords: quinoxaline; α-haloketones; synthesis; cyclo-condensation; thiazino[2,3-b]quinoxaline

Studies on the synthesis and chemistry of new quinoxalines have attracted considerable attention in the past 10 years because of their interesting chemical as well as biological properties.[1] Quinoxalines have anti-viral,[2] anti-bacterial,[3] anti-inflammatory,[4] anti-protozoal,[5] anti-cancer,[6] anti-depressant,[7] anti-HIV activity[8] and are also kinase inhibitors.[9] They are used in the agricultural area as fungicides, herbicides, and insecticides.[1] Furthermore quinoxaline units are present in the structure of various antibiotics such as echinomycin, levomycin and actinoleutin, which are known to inhibit the growth of gram positive bacteria and are active against various transplantable tumours.[10,11] In addition, quinoxaline derivatives are used in dyes,[12] efficient electron luminescent materials,[13] organic semiconductors,[14] chemically controllable switches,[15] building blocks for the synthesis of anion receptors,[16] cavitands[17] and dehydroannulenes.[18] They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition.[19] Some quinoxaline derivatives have been synthesised using microwave irradiation.[20] However, recent synthetic methods have focused on techniques involving alternative activation modes. Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 1,2-diamines with α-diketones,[1] 1,4-addition of 1,2-diamines[21] to diazenylbutenes,[22] cyclisation–oxidation of phenacyl bromides and oxidative coupling of epoxides with ene-1,2-diamines.[23–25] Since quinoxalines are biologically important compounds, they have been the subject of our recent investigations. We now report a convenient and straightforward method for the synthesis of new thiazino[2,3-b]quinoxaline derivatives and a new heterocyclic system, 3-methyl-1,4-dihydropyrazolo[4′,3′:5,6][1,4]thiazino[2,3-b]quinoxaline**.**

Results and discussion

3-Aminoquinoxaline-2-thiol (**1**) was prepared according to the literature procedure.[26] We initially reacted this compound with phenacyl bromide (**2b)** under different reaction conditions. The excellent conversion of the starting materials (**1** and **2b**) into their product **3b** was achieved within two hours in refluxing acetic acid (Scheme 1).

Under the optimised conditions, the cyclo-condensation of a wide range of aryl α-haloketones carrying either electron-donating or electron-withdrawing substituents on their aromatic rings, with 3-aminoquinoxaline-2-thiol proceeded smoothly and gave the corresponding thiazino[2,3-b]quinoxaline derivatives (**3b–g**) in good to excellent yields. The phenacyl bromides containing electron-withdrawing substituents tended to react at higher rates with shorter reaction times (**2e–g**) in comparison with those having electron-donating substituents (**2b–d**) (Table 1).



Scheme 1 General route for the synthesis of thiazino[2,3-b]quinoxaline.

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The structural assignment of compounds **3a–g** and **5** is based upon spectroscopic and microanalytical data. For example, the ^{1}H NMR spectrum of 3-(4-methoxyphenyl)-4H-[1,4] thiazino[2,3-b]quinoxaline **(3e)** showed two singlet peaks at δ 3.82 and 5.47 ppm belonging to methyl groups of the methoxy and CH of thiazin ring, respectively. The multiplet signals in the range of δ 6.94–7.72 ppm correspond to the aromatic ring protons. The IR spectrum was devoid of the NH_2 absorption bands at ν 3264 and 3395 cm^{-1} of the precursor, but an absorption band at ν 3199 cm^{-1} demonstrated the existence of the NH group in the product **3e**. The mass spectrum of **3e** showed a molecular ion signal at *m/z* 307 (M^+) corresponding to the molecular formula $C_{17}H_{13}N_3OS$.

Table 1 Synthesis of new thiazino[2,3-b]quinoxaline derivatives

Compound	R	Time/h	Yield/%
3a	CH_3	2.15	89
3b	Ph	2	82
3c	*p*-C_6H_4–Me	2.10	87
3d	*p*-C_6H_4–OMe	2.20	79
3e	*p*-C_6H_4–Ph	1.50	99
3f	*p*-C_6H_4–Br	1.50	80
3g	*p*-C_6H_4–NO_2	1.45	89

Conclusion

In summary, we have successfully developed a simple and efficient method for the synthesis of new thiazino[2,3-b] quinoxaline derivatives from 3-aminoquinoxaline-2-thiol and various α-haloketones using acetic acid. Similar reaction with 4-bromo-3-methyl-4,5-dihydro-1H-5-pyrazolone gave a new heterocyclic system, 3-methyl-1,4-dihydropyrazolo [4′,3′:5,6] [1,4] thiazino [2,3-b]quinoxaline.

Experimental

Reactions were monitored by TLC and melting points were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. FT-IR spectra were recorded using KBr disks on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. The ^{1}H NMR (400 MHz) spectra were recorded on a Bruker AC 400 spectrometer using $CDCl_3$ or DMSO as a solvent, chemical shifts have been expressed in ppm downfield from TMS. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyser.

Synthesis of 3-aminoquinoxaline-2-thiol (**1**)

Compound (**1**) was prepared by the literature procedure. Yield 73%; m.p. > 300 °C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.02 (s, 2H, NH_2), 7.23–7.45 (m, 4H, Ar), 14.33 (s, 1H, SH); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 115.9, 124.7,125.0, 126.5, 128.2, 136.5, 154.3, 168.2; IR (KBr disc): ν 3395, 3264, 1450, 1359 cm^{-1}.; MS (*m/z)* 177 (M^+). Anal. calcd for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71; S, 18.09; found: C, 54.02; H, 3.64; N, 23.36; S, 17.85%.

*Synthesis of compounds (***3a–g** *and* **5***); general procedure*

A mixture of 2-amino-3-quinoxalinethiol (0.177 g, 1 mmol) and the appropriate α-haloketones (1 mmol) in glacial acetic acid (10 mL) was heated under reflux for the appropriate time. The solvent was evaporated under reduced pressure and the precipitate was collected and recrystallised from ethanol.

3-Methyl-4H-[1,4]thiazino[2,3-b]quinoxaline (**3a**): Yield 89%; m.p. 196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3), 5.46 (s, 1H, CH), 7.39–7.76 (m, 4H, Ar), 11.87 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 16.57, 98.84, 128.31, 128.81, 128.97, 131.61, 133.71, 136.41, 139.62, 146.29, 147.67; IR (KBr disc): ν 3215, 3056, 2982, 2917, 1673, 1640, 1135 cm^{-1}.; MS (*m/z)* 215 (M^+). Anal. calcd for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52; S, 14.89; found: C, 61.10; H, 4.11; N, 19.01; S, 14.16%.

3-Phenyl-4H-[1,4]thiazino[2,3-b]quinoxaline (**3b**): Yield 92%; m.p. 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (s, 1H, CH), 7.78–7.66 (m, 9H, Ar), 12.26 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 108, 120.74, 125.95, 127.84, 128.56, 129.02, 130.68, 132.49, 132.97, 134.31, 135.78, 141.09, 147.17, 152.69; IR (KBr disc): ν 3187, 3020, 2974, 2869, 1648, 1598, 1121 cm^{-1}.; MS (*m/z)* 277 (M^+). Anal. calcd for $C_{11}H_9N_3S$: C, 69.29; H, 4.00; N, 15.15; S, 11.56; found: C, 69.01; H, 3.87; N, 15.02; S, 11.00%.

3-(p-Tolyl)-4H-[1,4]thiazino[2,3-b]quinoxaline (**3c**): Yield 95%; m.p. 213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 5.44 (s, 1H, CH), 7.02–7.65 (m, 8H, Ar), 11.64 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.19, 108.16, 121.74, 129.34, 129.87, 130.64, 130.99, 131.09, 134.51, 136.10, 136.54, 138.48, 140.19, 144.52, 151.35; IR (KBr disc): ν 3214, 3048, 2916, 2864, 1697, 1621, 1121 cm^{-1}.; MS (*m/z)* 291 (M^+). Anal. calcd for $C_{17}H_{13}N_3S$: C, 70.08; H, 4.50; N, 14.42; S, 11.00; found: C, 70.32; H, 4.88; N, 14.87; S, 11.66%.

3-(4-Methoxyphenyl)-4H-[1,4]thiazino[2,3-b]quinoxaline (**3d**): Yield 96%; m.p. 248 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, CH_3), 5.47 (s, 1H, CH), 6.94–7.72 (m, 8H, Ar), 11.17 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 55.45, 96.36, 114.71, 118.07, 123.58, 126.44, 127.72, 128.90, 131.35, 132.64, 135.45, 138.56, 143.46, 151.67, 161.17; IR (KBr disc): ν 3199, 3035, 2929, 2839, 1633, 1604, 1137 cm^{-1}.; MS (*m/z)* 307 (M^+). Anal. calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67; S, 10.43; found: C, 66.12; H, 4.02; N, 13.27; S, 9.87%.

3-([1,1′-Biphenyl]-4-yl)-4H-[1,4]thiazino[2,3-b]quinoxaline (**3e**): Yield 100%; m.p. 241 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (s, 1H, CH), 7.22–7.66 (m, 13H, Ar), 12.21 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 109.00, 122.65, 124.32, 126.41, 127.32, 127.98, 128.34, 128.61, 128.97, 129.53, 132.27, 133.98, 135.79, 139.45, 142.39, 134.21, 147.15, 154.28; IR (KBr disc): ν 3076, 2978, 2851, 1630, 1606, 1135 cm^{-1}; MS (*m/z)* 353 (M^+). Anal. calcd for $C_{22}H_{15}N_3S$: C, 74.76; H, 4.28; N, 11.89; S, 9.07; found: C, 74.09; H, 4.02; N, 11.41; S, 8.77%.

3-(4-Bromophenyl)-4H-[1,4]thiazino[2,3-b]quinoxaline (**3f**): Yield 96%; m.p. 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (s, 1H, CH), 7.21–7.61 (m, 8H, Ar), 11.34 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 100.96, 116.67, 117.58, 126.47, 129.83, 130.56, 131.15, 131.49, 132.36, 134.62, 135.24, 138.67, 142.36, 152.47; IR (KBr disc): ν 3197, 3033, 2917, 1668, 1636, 1135 cm^{-1}.; MS (*m/z)* 356 (M^+). Anal. calcd for $C_{16}H_{10}BrN_3S$: C, 53.94; H, 2.83;N, 11.80; S, 9.00; found: C, 53.46; H, 2.71; N, 11.18; S, 8.30%.

3-(4-Nitrophenyl)-4H-[1,4]thiazino[2,3-b]quinoxaline (**3g**): Yield 80%; m.p. 261 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 7.48–7.65 (m, 8H), 11.87 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 102.785, 120.56, 124.53, 126.95, 127.06, 128.25, 129.65, 131.53, 132.26, 134.98, 145.53, 146.34, 149.16, 105.42; IR (KBr disc): ν 3178, 3031, 2920, 2840, 1642, 1612, 1129 cm^{-1}.; MS (*m/z)* 356 (M^+). Anal. calcd for $C_{16}H_{10}N_4O_2S$: C, 59.62; H, 3.13; N, 17.38; S, 9.95; found: C, 59.21; H, 3.03; N, 16.99; S, 9.37%.

3-methyl-1,11-dihydropyrazolo[3′,4′:5,6][1,4]thiazino[2,3-b] quinoxaline (**5**): Yield 89%; m.p. 306 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 7.26–7.39 (m, 4H, Ar), 10.35 (s, 1H, NH), 11.91 (s, 1H, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 19.32, 119.65, 125.46, 127.65, 128.37, 129.93, 131.24, 135.72, 139.74, 142.71, 145.26, 158.43; IR (KBr disc): ν 3235, 3203, 3125, 3051, 2839, 1671, 1070 cm^{-1}.; MS (*m/z)* 255 (M^+). Anal. calcd for $C_{12}H_9N_5S$: C, 56.45; H, 3.55; N, 27.43; S, 12.56; found: C, 56.13; H, 3.00; N, 26.98; S, 12.013%.

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