

Novel Catalyst-Free Synthesis of Some 3-Alkylaminoquinoxaline-2(1H)-thiones and 3-Alkyloxyquinoxaline-2(1H)-thiones in Ethanol

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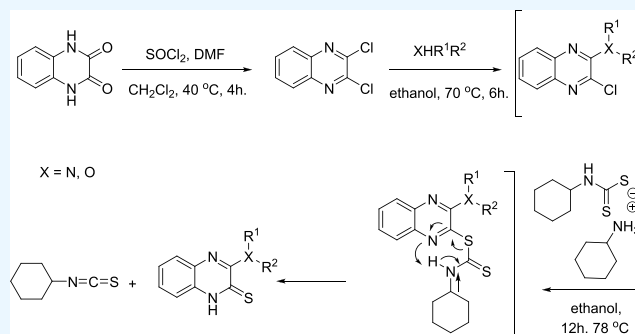


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ABSTRACT: Seventeen 3-alkylaminoquinoxaline-2(1H)-thiones and 3-alkyloxyquinoxaline-2(1H)-thiones were prepared by a novel thionation protocol from the readily available quinoxaline-2,3-dione in excellent overall yields. This protocol starts with the chlorination of dione using thionyl chloride to give 2,3-dichloroquinoxaline followed by the reaction with equimolar amounts of *N*-nucleophiles (primary amines and secondary amines) or *O*-nucleophiles (phenols and alcohols) to principally afford 2-alkanamino-3-chloroquinoxalines or 2-alkyloxy-3-chloroquinoxalines, respectively. The chloroquinoxalines reacted with the thionation reagent *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt in ethanol under reflux to principally give the corresponding quinoxalin-2-yl cyclohexylcarbamodithioate that finally rearranges *in situ* to give the corresponding thiones in 76–93% overall yields. Our novel catalyst-free synthesis of some 3-alkylaminoquinoxaline-2(1H)-thiones and 3-alkyloxyquinoxaline-2(1H)-thiones in ethanol protocol has many advantages compared with traditional methods: excellent yields, one-pot reaction, simple experimental procedure, and commercial availability of the required reagents. In addition, this method could be generalized to involve a wide range of amines, phenols, and alcohols, and also during the reaction, we did not notice a bad odor. The structures of synthesized compounds are elucidated via different methods such as ¹H NMR, ¹³C NMR, elemental analysis, and MS.



INTRODUCTION

Quinoxaline is a biologically diverse scaffold with wide applications in chemical and pharmaceutical chemistry. Quinoxaline is excessively found in natural products and pharmaceutical chemicals.^{1–4} Quinoxaline thiones, which include an intriguing thioamide functional group, are employed to modify the structure of this framework. Our research group was able to successfully modify the structure of many heterocycles on the basis of thioamides' chemoselective reactions.^{5–10} Despite the extensive research on quinoxaline, we found a few articles that described the preparation of quinoxaline thiones. The three-component reaction of *o*-phenylenediamines, sulfur, and acetophenones in DMSO in the presence of piperidine, and phenyl acetylenes with elemental sulfur and *o*-phenylenediamine in the presence of DABCO afforded 3-arylquinoxaline-2-thiones.^{11,12} Additionally, 3-alkylquinoxalin-2(1H)-one might be thionated using phosphorus pentasulfide in refluxing pyridine to provide 3-alkylquinoxaline-2(1H)-thione.¹³ Reacting 2-chloro-3-alkylquinoxaline with thiourea in ethanol under reflux conditions gave an alternate method for producing 3-alkylquinoxaline-2(1H)-thione.¹⁴ On the other hand, 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one was thoroughly studied and was made by reacting arylisothiocyanates, methyl 3-((phenylcarbamothioyl)thio)propanoate, and aryl dithiocarba-

mic acid with substrates such as isatoic anhydride, anthranilic acid, anthranilamide, and methyl anthranilate.^{15–18} Open chain thioamides are great starting materials for creating various sulfur-heterocyclic compounds. Thioamides were prepared from ketoxime in the presence of dehydrating agents via Beckmann rearrangement procedure¹⁹ or a three-component reaction with the catalyst aniline, aldehydes, and elemental sulfur powder via a modified Willgerodt–Kindler reaction.²⁰ Using thionating reagents, Lawesson's reagent,²¹ and P₄S₁₀^{22,23} in dry toluene, xylene, or pyridine under reflux conditions gave an additional procedure for amide–thioamide transformations.

Although several of these methods are highly intriguing and exhibit great yields, their applicability has been constrained by significant limitations such as severe reaction conditions, long reaction times, requirement for some specific reagents of high costs, ultradry solvents, and unpleasant odors. Earlier, we innovated an interesting two-step thionation protocol of

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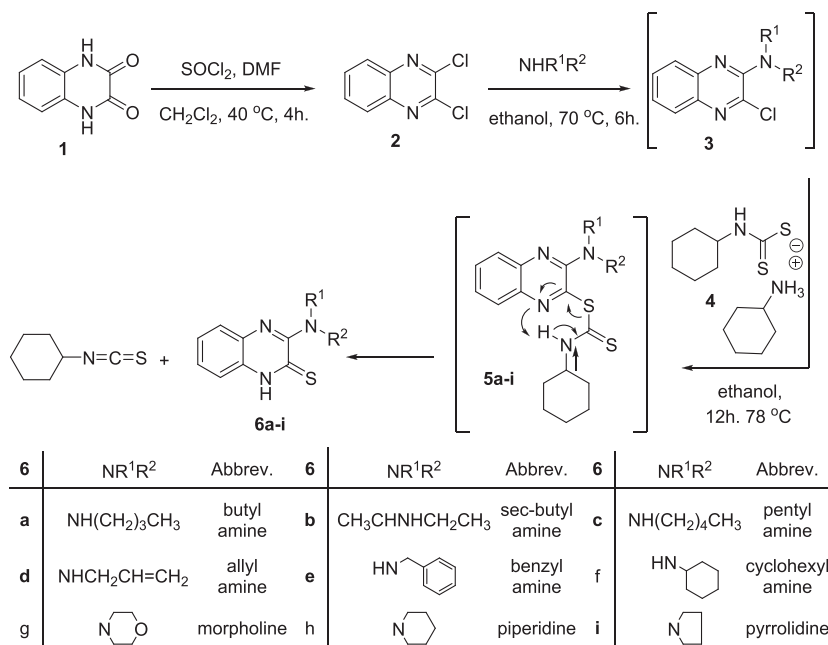
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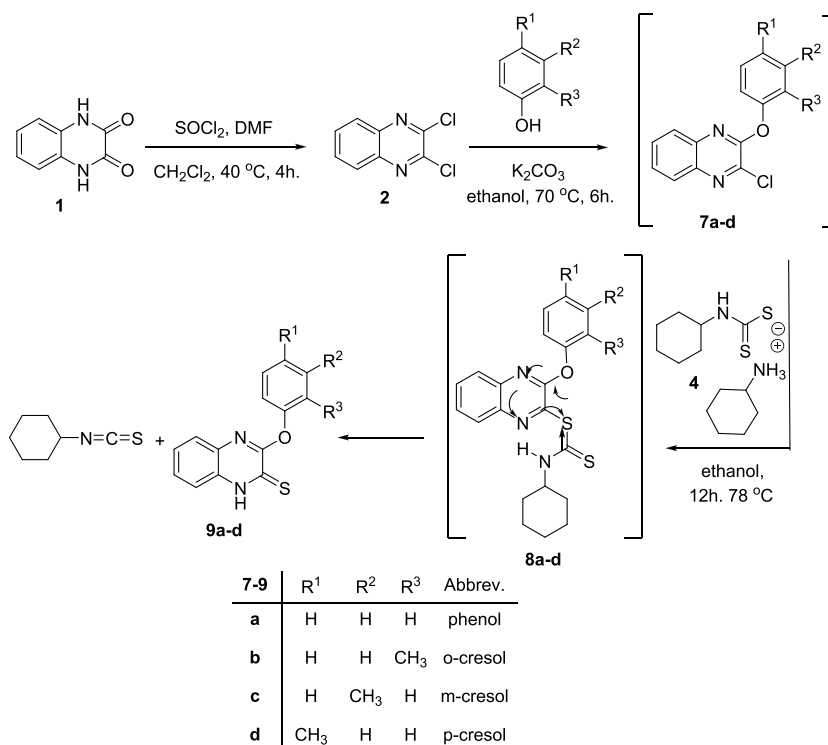
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Scheme 1. Preparation of 3-Alkylaminoquinoxaline-2(1H)-thiones 6a–i



Scheme 2. Preparation of 3-Aryloxyquinoxaline-2(1H)-thiones 9a–d

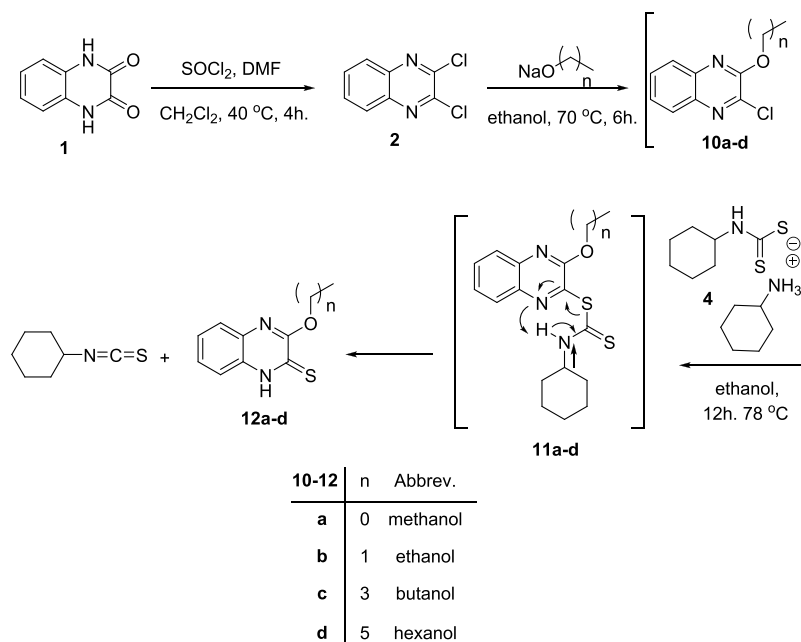


heterocyclic amides starting by chlorination of heterocyclic amides and the subsequent reaction with the thionation reagent simply prepared from cyclohexyl amine and carbon disulfide^{24–28} under mild conditions. Herein, we wish to synthesize a number of 3-alkylaminoquinoxaline-2(1H)-thiones and 3-alkyloxyquinoxaline-2(1H)-thiones based on the conversion of heterocyclic amides into heterocyclic thioamides using a thionation reagent derived from cyclohexyl amine and carbon disulfide.

RESULTS AND DISCUSSION

Quinoxaline-2,3-dione **1** is an interesting precursor simply prepared by the reaction of oxalic acid with *o*-phenylenediamine.²⁹ Chlorination of quinoxaline-2,3-dione **1** using thionyl chloride in the presence of dimethylformamide in methylene chloride for 4 h afforded 2,3-dichloroquinoxaline (**2**) in good to excellent yields.³⁰ The reaction of 2,3-dichloroquinoxaline (**2**) with equimolar amounts of primary and secondary amines in ethanol for 6 h at 70 °C principally gave 2-alkanamino-3-chloroquinoxalines **3a–i** that were used *in situ* without

Scheme 3. Preparation of 3-Alkoxyquinoxaline-2(1H)-thiones 12a–d



isolation (Scheme 1). 2-Alkanamino-3-chloroquinoxalines 3a–i are excellent precursors to apply our novel thiation protocol and the formation of 3-alkylaminoquinoxaline-2(1H)-thiones. Thus, the reaction of ethanolic solution of the *in situ* generated 2-alkanamino-3-chloroquinoxalines 3a–i with *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (4) at 78 °C for 12 h principally afforded the *in situ* generated active 3-alkanaminooquinoxalin-2-yl cyclohexylcarbomodithioates (5a–i) that spontaneously rearrange to form the desired products 3-alkylaminoquinoxaline-2(1H)-thiones 6a–i in 67–92% yields (Scheme 1). Compounds 3-alkanaminooquinoxalin-2-yl cyclohexylcarbomodithioates (5a–i) were presumed to have an intramolecular hydrogen bond between the cyclohexyl NH and the N1 of the quinoxaline nitrogen of the type cyclohexyl-NH...N=C. The presence of the neighboring cyclohexyl group with an electron-donating behavior facilitates the abstraction of the hydrogen by the quinoxaline N1 atom with an overall C–S bond cleavage and the formation of cyclohexyl isothiocyanate (Scheme 1). The preparation of 3-alkylaminoquinoxaline-2(1H)-thiones 6a–i via our novel thiation process has the advantages of one-pot reaction, operation simplicity, easy workup, available reagents, no bad odor, and finally excellent yields. Keivanloo et al.^{31,32} reported the synthesis of 3-morpholinoquinoxaline-2(1H)-thione (6g) by the reaction of 4-(3-chloroquinoxalin-2-yl)morpholine with Na₂S·9H₂O in DMF at room temperature for 3 h, and they stated that further purification was not necessary. The thione 6g was produced in 70% yield, and the reported melting point was 56–58 °C.^{31,32} We should note that our attempts following this reaction condition gave the thione 6g with interfering bis(3-morpholinoquinoxalin-2-yl)-sulfane, and the reported melting point reflects the low purity of the product.

The structure assignments of 3-alkylaminoquinoxaline-2(1H)-thiones 6a–i were based on ¹H and ¹³C NMR and MALDI mass spectral analysis. Thus, the ¹H NMR spectrum of 3-(benzylamino)quinoxaline-2(1H)-thione (6e) showed signals at δ 4.71, 7.96, and 14.33 ppm corresponding to CH₂,

NHCH₂, and NHCS groups, respectively. The ¹³C NMR spectrum of 6e showed signals at δ 44.9, 152.3, and 169.0 ppm corresponding to CH₂, C=N and C=S groups, respectively.

2-Alkanamino-3-chloroquinoxalines 3a–i proved to be excellent precursors for the application of our novel thiation process and the formation of 3-alkylaminoquinoxaline-2(1H)-thiones 6a–i in good yields. We found it interesting to modify the structure of the quinoxaline ring by the introduction of alkoxy groups followed by thiation to give 3-alkoxyquinoxaline-2(1H)-thiones. Thus, 2,3-dichloroquinoxaline (2) reacted with equimolar amounts of a number of phenols in the presence of potassium carbonate in ethanol at 70 °C for 6 h to afford 2-aryloxy-3-chloroquinoxalines 7a–d, used *in situ* without further isolation (Scheme 2). 2-Aryloxy-3-chloroquinoxalines 7a–d are excellent precursors for the formation of quinoxaline thiones by our novel thiation protocol. Thus, 3-chloroquinoxalines 7a–d reacted with *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (4) in ethanol at 78 °C for 12 h to principally produce 3-aryloxyquinoxalin-2-yl cyclohexylcarbomodithioates 8a–d that rearrange to finally give 3-aryloxyquinoxaline-2(1H)-thiones 9a–d in excellent yields (Scheme 2).

On the other hand, 2-alkoxy-3-chloroquinoxalines 10a–d were prepared by the reaction of sodium alkoxides (prepared by the reaction of sodium with alcohols: methanol, ethanol, butanol, and hexanol) with 2,3-dichloroquinoxaline (2) in absolute ethanol. Similarly, 2-alkoxy-3-chloroquinoxalines 10a–d were reacted *in situ* with *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (4) in ethanol for 6 h and principally gave 3-alkoxyquinoxalin-2-yl cyclohexylcarbomodithioates 11a–d that rearrange to finally give 3-alkoxyquinoxaline-2(1H)-thiones 12a–d in excellent yields (Scheme 3).

The structure assignment of 3-aryloxyquinoxaline-2(1H)-thiones 9a–d and 3-alkoxyquinoxaline-2(1H)-thiones 12a–d was based on ¹H and ¹³C NMR and MALDI mass spectral analysis. Thus, the ¹H NMR spectrum of 3-(*p*-tolylloxy)quinoxaline-2(1H)-thione (9d) showed two singlet signals δ 2.36 and 14.52 ppm corresponding to CH₃ and NH groups,

respectively. The ^{13}C NMR spectrum of **9d** showed signals δ 20.9, 157.8, and 169.6 ppm corresponding to CH_3 , $\text{C}=\text{N}$, and $\text{C}=\text{S}$ groups, respectively. On the other hand, the ^1H NMR spectrum of 3-ethoxyquinoxaline-2(1H)-thione (**12b**) showed signals at δ 1.40, 4.45, and 14.31 ppm corresponding to CH_3 , CH_2 , and NH groups, respectively. The ^{13}C NMR spectrum of **12b** showed signals at 14.5, 63.8, 151.7, and 170.0 ppm corresponding to CH_3 , OCH_2 , $\text{C}=\text{N}$, and $\text{C}=\text{S}$ groups, respectively. The ^1H NMR spectra of all synthesized quinoxaline thiones gave a singlet signal at 14.50 ppm corresponding to the NH group, which indicates that the NH is taking part in an intermolecular hydrogen bond interaction of the type $\text{NH}\cdots\text{S}=\text{C}$.

CONCLUSIONS

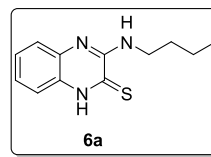
An interesting protocol was used for the synthesis of 3-alkylaminoquinoxaline-2(1H)-thiones and 3-alkyloxyquinoxaline-2(1H)-thiones. The products were obtained from readily available quinoxaline-2,3-dione starting by chlorination using thionyl chloride followed by the reaction with nucleophiles amines, alcohols, and phenols and finally the reaction with thionation reagent *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt. This protocol has the advantages of one-pot reaction, operation simplicity, available reagents, no bad odor, and generalization to involve a wide range of amines, phenols, and alcohols.

EXPERIMENTAL SECTION

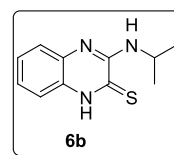
General techniques for the experimental procedures that involve solvents, TLC detection, elemental analysis instrument, melting point apparatus, NMR, solvents, internal standard, apparatus, and place of analysis are introduced with the supplementary data. The quinoxaline-2,3-dione **1** was prepared according to the reported literature,²⁹ and *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt was prepared according to the reported literature.²⁴

Preparation of 2,3-Dichloroquinoxaline (2).³⁰ Quinoxaline-2,3-dione **1** (0.8 g, 5 mmol) solution in dry methylene chloride (5 mL) was mixed with thionyl chloride (1.2 g, 10 mmol). DMF (0.5 mL) was added dropwise to the stirred reaction mixture. The reaction mixture was heated at 40 °C for 6 h and then cooled. The reaction mixture was poured over crushed ice with vigorous stirring. Methylene chloride was used to extract the reaction mixture followed by sodium carbonate washing and sodium sulfate drying. The methylene chloride extract was evaporated under reduced pressure and was chromatographed using ethyl acetate pet. ether as eluent.

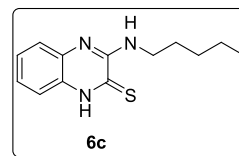
General Procedure for Preparation of 3-Alkylaminoquinoxaline-2(1H)-thiones 6a–i.^{22,31,32} A mixture of amine (2 mmol), butyl amine, *sec*-butyl amine, pentyl amine, allyl amine, benzyl amine, cyclohexyl amine, morpholine, piperidine, pyrrolidine, and 2,3-dichloroquinoxaline **2** (1 mmol, 0.2 g) in ethanol was heated at 70 °C for 6 h (TLC monitored for full consumption of dichloroquinoxaline) to give 2-alkanamino-3-chloroquinoxaline **3**, which was used without isolation or purification. To the ethanol solution of **3** was added *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (**4**) (1 mmol, 0.28 g), and the reaction mixture was refluxed for a further 12 h. The reaction mixture was cooled, and the obtained yellow crystals described as 3-alkylaminoquinoxaline-2(1H)-thiones **6a–i** were collected by filtration without any further purification.



3-(Butylamino)quinoxaline-2(1H)-thione (6a). Yellow crystals, yield 85%, mp 202–203 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (*J*, Hz): 0.91–0.95 (m, 3 H, CH_3), 1.18–1.22 (m, 2 H, CH_2), 1.39–1.43 (m, 2 H, CH_2), 3.49–3.52 (m, 2 H, NCH_2), 7.24 (t, 2 H, *J* = 8.0 Hz, Ar–H), 7.33 (d, 1 H, *J* = 8.0 Hz, Ar–H), 7.46 (d, 1 H, *J* = 8.0 Hz, Ar–H), 7.92–7.95 (m, 1 H, NH), 14.31 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 16.8 (CH_3), 22.7 (CH_2), 32.1 (CH_2), 42.6 (NCH_2), 116.1 (CHAr), 126.2 (CHAr), 126.7 (CHAr), 127.9 (CHAr), 130.3 (Cq), 134.1 (Cq), 151.6 (C = N), 170.2 (C = S). MS (MALDI, positive mode, matrix DHB) *m/z*: (*M* + Na)⁺. 356.30 Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{S}$ (233.3) C, 61.77; H, 6.48; N, 18.01; S, 13.74. Found: C, 61.80; H, 6.53; N, 18.06; S, 13.78

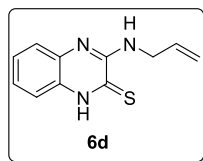


3-(*sec*-Butylamino)quinoxaline-2(1H)-thione (6b). Yellow crystals, yield 76%, mp 182–183 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (*J*, Hz): 0.92–0.94 (m, 3 H, CH_3), 1.76–1.80 (m, 2 H, CH_2), 3.01–3.05 (m, 1 H, NCH), 7.24 (t, 2 H, *J* = 8.0 Hz, Ar–H), 7.33 (d, 1 H, *J* = 8.0 Hz, Ar–H), 7.45 (d, 1 H, *J* = 8.0 Hz, Ar–H), 7.91–7.94 (m, 1 H, NH), 14.30 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 14.7 (CH_3), 23.2 (CH_3), 29.6 (CH_2), 47.8 (NCH_2), 116.3 (CHAr), 126.1 (CHAr), 126.8 (CHAr), 127.7 (CHAr), 130.1 (Cq), 134.2 (Cq), 151.8 (C = N), 169.8 (C = S). MS (MALDI, positive mode, matrix DHB) *m/z*: (*M* + Na)⁺. 256.32 Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{S}$ (233.3) C, 61.77; H, 6.48; N, 18.01; S, 13.74. Found: C, 61.82; H, 6.52; N, 18.04; S, 13.77

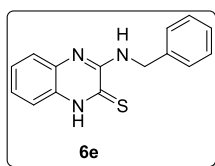


3-(Pentylamino)quinoxaline-2(1H)-thione (6c). Yellow crystals, yield 88%, mp 189–190 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (*J*, Hz): 0.89–0.91 (m, 3 H, CH_3), 1.16–1.20 (m, 2 H, CH_2), 1.23–1.26 (m, 2 H, CH_2), 1.37–1.40 (m, 2 H, CH_2), 3.46–3.51 (m, 2 H, NCH_2), 7.25 (t, 2 H, *J* = 8.0 Hz, Ar–H), 7.30 (d, 1 H, *J* = 8.0 Hz, Ar–H), 7.41 (d, 1 H, *J* = 8.0 Hz, Ar–H), 7.87–7.90 (m, 1 H, NH), 14.34 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 16.8 (CH_3), 23.4 (CH_2), 27.1 (CH_2), 31.6 (CH_2), 43.1 (NCH_2), 116.2 (CHAr), 126.4 (CHAr), 126.6 (CHAr), 127.8 (CHAr), 130.2 (Cq), 134.1 (Cq), 151.5 (C = N), 169.9 (C = S). MS (MALDI, positive mode, matrix DHB) *m/z*: (*M* + Na)⁺. 270.3 Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{S}$ (247.3) C, 63.12; H, 6.93; N, 16.99; S, 12.96. Found: C, 63.16; H, 6.97; N, 17.05; S, 13.02.

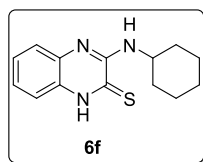
3-(Allylamino)quinoxaline-2(1H)-thione (6d). Yellow crystals, yield 67%, mp 176–178 °C. ^1H NMR spectrum (400



MHz, DMSO), δ , ppm (J , Hz): 4.12–4.16 (m, 2 H, CH₂), 5.06–5.09 (m, 1 H, CH₂), 5.64–5.72 (m, 1 H, CH), 7.22 (t, 2 H, J = 8.0 Hz, Ar–H), 7.32 (d, 1 H, J = 8.0 Hz, NH), 7.47 (t, 1 H, J = 8.0 Hz, Ar–H), 7.83–7.97 (m, 1 H, NH), 14.30 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 40.8 (NCH₂), 116.1 (CHAr), 118.3 (CH₂), 124.3 (CHAr), 125.6 (CHAr), 126.3 (CHAr), 127.5 (Cq), 133.5 (CH), 136.7 (Cq), 151.2 (C = N), 170.1 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 240.31 Anal. Calcd for C₁₁H₁₁N₃S (217.3) C, 60.80; H, 5.10; N, 19.34; S, 14.75. Found: C, 60.84; H, 5.13; N, 19.38; S, 14.81.

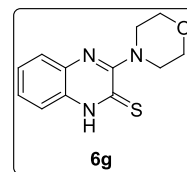


3-(Benzylamino)quinoxaline-2(1H)-thione (6e). Yellow crystals, yield 92%, mp 210–211 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 4.71 (d, 2 H, J = 6.0 Hz, CH₂), 7.21–7.48 (m, 9 H, 9 Ar–H), 7.96 (t, 1 H, J = 6.0 Hz, NH), 14.33 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 44.9 (NCH₂), 116.2 (CHAr), 124.6 (Cq), 125.6 (CHAr), 126.4 (CHAr), 127.3 (CHAr), 127.9 (CHAr), 128.0 (2CHAr), 128.8 (2CHAr), 136.6 (Cq), 139.7 (Cq), 152.3 (C = N), 169.0 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 290.3 Anal. Calcd for C₁₅H₁₃N₃S (267.4) C, 67.39; H, 4.90; N, 15.72; S, 11.99. Found: C, 67.43; H, 4.95; N, 15.76; S, 12.03.

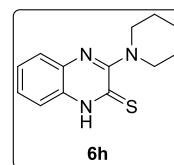


3-(Cyclohexylamino)quinoxaline-2(1H)-thione (6f). Yellow crystals, yield 85%, mp 234–235 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 1.38–1.62 (m, 6 H, 3CH₂), 1.74–1.97 (m, 4 H, 2CH₂), 3.95–4.00 (m, 1 H, CH), 7.23 (t, 2 H, J = 8.0 Hz, Ar–H), 7.30–7.33 (m, 1 H, NH), 7.47 (d, 2 H, J = 8.0 Hz, Ar–H), 14.33 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 24.8 (2CH₂), 25.7 (CH₂), 32.2 (2CH₂), 49.6 (CH), 116.2 (CHAr), 124.4 (CHAr), 125.5 (CHAr), 126.5 (CHAr), 127.7 (Cq), 136.8 (Cq), 151.4 (C = N), 169.9 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 282.3 Anal. Calcd for C₁₄H₁₇N₃S (259.4) C, 64.83; H, 6.61; N, 16.20; S, 12.36. Found: C, 64.86; H, 6.66; N, 16.24; S, 12.42.

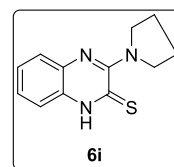
3-Morpholinoquinoxaline-2(1H)-thione (6g).^{31,32} Yellow crystals, yield 90%, mp 205–206 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 3.74–3.78 (m, 8 H, 4CH₂), 7.34–7.39 (m, 2 H, Ar–H), 7.49–7.59 (m, 2 H, Ar–H), 14.14 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 48.9 (2NCH₂), 66.3 (2OCH₂), 115.7 (CHAr), 126.2 (CHAr),



126.6 (CHAr), 127.0 (CHAr), 130.0 (Cq), 135.4 (Cq), 157.4 (C = N), 170.0 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 270.3 Anal. Calcd for C₁₂H₁₃N₃OS (247.3) C, 58.28; H, 5.30; N, 16.99; S, 12.96. Found: C, 58.33; H, 5.34; N, 17.05; S, 13.00.



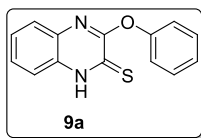
3-Piperidinoquinoxaline-2(1H)-thione (6h). Yellow crystals, yield 84%, mp 182–183 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 1.62–1.86 (m, 6 H, 3CH₂), 3.52–3.96 (m, 4 H, 2NCH₂), 7.29–7.34 (m, 2 H, 2Ar–H), 7.46–7.55 (m, 2 H, 2Ar–H), 14.10 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 24.3 (CH₂), 25.7 (2CH₂), 48.2 (2NCH₂), 115.9 (CHAr), 126.0 (CHAr), 126.4 (CHAr), 127.7 (CHAr), 128.9 (Cq), 135.2 (Cq), 156.4 (C = N), 169.9 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 268.3 Anal. Calcd for C₁₃H₁₅N₃S (245.3) C, 63.64; H, 6.16; N, 17.13; S, 13.07. Found: C, 63.68; H, 6.21; N, 17.17; S, 13.12.



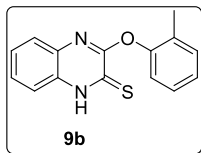
3-Pyrrolidinoquinoxaline-2(1H)-thione (6i). Yellow crystals, yield 78%, mp 187–188 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 1.32–1.54 (m, 4 H, 2CH₂), 2.64–2.73 (m, 4 H, 2CH₂), 7.23 (t, 2 H, J = 8.0 Hz, Ar–H), 7.47 (d, 2 H, J = 8.0 Hz, Ar–H), 14.11 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 25.3 (2CH₂), 48.6 (2NCH₂), 115.4 (CHAr), 125.8 (CHAr), 126.2 (CHAr), 127.0 (CHAr), 127.3 (Cq), 136.5 (Cq), 156.8 (C = N), 170.2 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 254.35 Anal. Calcd for C₁₂H₁₃N₃S (231.3) C, 62.31; H, 5.66; N, 18.17; S, 13.86. Found: C, 62.35; H, 5.69; N, 18.21; S, 13.92.

General Procedure for Synthesis of 3-aryloxyquinoxaline-2(1H)-thiones 9a–d. To a mixture of phenol (1.0 mmol), phenol, *o*-cresol, *m*-cresol, *p*-cresol, and potassium carbonate (0.139 g, 1 mmol) in ethanol 10 mL was added 2,3-dichloroquinoxaline **2** (1 mmol, 0.2 g). The reaction mixture was refluxed at 70 °C for 6 h until complete consumption of the 2,3-dichloroquinoxaline (TLC monitored) to give 2-aryloxy-3-chloroquinoxalines **7a–d**, which were used without isolation or purification. The reaction mixture was filtered, and *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (**4**) (1 mmol, 0.28 g) was added *in situ*. The reaction mixture was refluxed for further 12 h (TLC monitored). The reaction mixture was cooled, and the obtained yellow crystals described

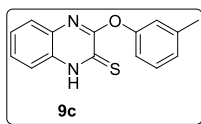
as 3-aryloxyquinoxaline-2(1H)-thiones **9a–d** were collected and filtered without any further purification.



3-Phenoxyquinoxaline-2(1H)-thione (9a). Yellow crystals, yield 76%, mp 228–229 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 7.13 (t, 2 H, J = 8.0 Hz, Ar–H), 7.22 (d, 2 H, J = 8.0 Hz, Ar–H), 7.43–7.61 (m, 5 H, Ar–H), 14.48 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 115.6 (2CHAr phenol), 116.2 (CHArQ), 121.3 (CHAr phenol), 125.9 (2CHAr phenol), 126.9 (CHArQ), 128.7 (CHArQ), 129.3 (CHArQ), 130.6 (2CHAr phenol), 131.5 (Cq), 133.6 (Cq), 135.2 (Cq), 153.2 (Cq), 158.4 (C = N), 169.9 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : ($M + \text{Na}$) $^+$. 277.3 Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{OS}$ (254.3) C, 66.12; H, 3.96; N, 11.02; S, 12.61. Found: C, 66.16; H, 4.01; N, 11.05; S, 12.66.

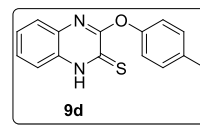


3-(o-Tolyloxy)quinoxaline-2(1H)-thione (9b). Yellow crystals, yield 89%, mp 222–223 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 2.21 (s, 3 H, CH_3), 7.07 (d, 2 H, J = 8.0 Hz, Ar–H), 7.26 (d, 2 H, J = 8.0 Hz, Ar–H), 7.27–7.31 (m, 1 H, Ar–H), 7.38–7.49 (m, 3 H, Ar–H), 14.55 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 20.7 (CH_3), 115.3 (CHAr), 116.4 (CHAr), 121.8 (CHAr), 125.6 (CHAr), 126.8 (CHAr), 128.3 (CHAr), 129.9 (CHAr), 131.7 (CHAr), 132.3 (Cq), 133.2 (Cq), 135.9 (Cq), 153.6 (Cq), 158.8 (C = N), 169.4 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : ($M + \text{Na}$) $^+$. 291.3 Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{OS}$ (268.3) C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.17; H, 4.54; N, 10.49; S, 12.01.



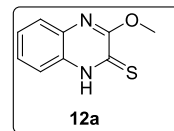
3-(m-Tolyloxy)quinoxaline-2(1H)-thione (9c). Yellow crystals, yield 78%, mp 229–230 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 2.33 (s, 3 H, CH_3), 6.86 (s, 1 H, Ar–H), 7.19 (d, 2 H, J = 8.0 Hz, Ar–H), 7.24 (d, 2 H, J = 8.0 Hz, Ar–H), 7.43–7.61 (m, 3 H, Ar–H), 14.47 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 21.3 (CH_3), 114.6 (CHAr), 115.2 (CHAr), 117.4 (CHAr), 121.8 (CHAr), 126.7 (CHAr), 127.9 (CHAr), 129.2 (CHAr), 130.9 (CHAr), 131.5 (Cq), 134.7 (Cq), 135.9 (Cq), 152.7 (Cq), 158.4 (C = N), 170.2 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : ($M + \text{Na}$) $^+$. 291.35 Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{OS}$ (268.3) C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.18; H, 4.55; N, 10.47; S, 11.99.

3-(p-Tolyloxy)quinoxaline-2(1H)-thione (9d). Yellow crystals, yield 93%, mp 238–239 °C. ^1H NMR spectrum (400

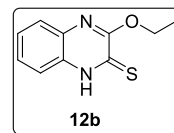


MHz, DMSO), δ , ppm (J , Hz): 2.36 (s, 3 H, CH_3), 7.12 (d, 2 H, J = 8.0 Hz, Ar–H), 7.28 (d, 2 H, J = 8.0 Hz, Ar–H), 7.30–7.35 (m, 1 H, Ar–H), 7.41–7.57 (m, 3 H, 3Ar–H), 14.52 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 20.9 (CH_3), 115.9 (CHAr), 121.9 (2CHAr), 126.2 (CHAr), 127.0 (CHAr), 128.6 (CHAr), 130.5 (2CHAr), 131.2 (Cq), 133.5 (Cq), 135.0 (Cq), 151.2 (Cq), 157.8 (C = N), 169.6 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : ($M + \text{Na}$) $^+$. 291.3 Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{OS}$ (268.3) C, 67.17; H, 4.56; N, 10.48; S, 12.01. Found: C, 67.14; H, 4.51; N, 10.44; S, 11.95.

General Procedure for the Preparation of 3-Alkoxyquinoxaline-2(1H)-thiones 12a–d. To a mixture of sodium alkoxide (1.0 mmol) (prepared by addition of sodium to alcohols methanol, ethanol, butanol, and hexanol portion-wise until the hydrogen gas was ceased and the consumption of sodium followed by evaporation of alcohol under reduced pressure until dryness) in ethanol 10 mL was added 2,3-dichloroquinoxaline **2** (1 mmol, 0.2 g). The reaction mixture was refluxed at 70 °C for 6 h until complete consumption of the 2,3-dichloroquinoxaline (TLC monitored) to give 3-alkoxyoxy-2-chloroquinoxalines **10a–d**, which were used without isolation or purification. The reaction mixture was filtered, and *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (**4**) (1 mmol, 0.28 g) was added *in situ*. The reaction mixture was refluxed for further 12 h (TLC monitored). The reaction mixture was cooled, and the obtained yellow crystals described as 3-alkoxyquinoxaline-2(1H)-thiones **12a–d** were collected and filtered without any further purification.

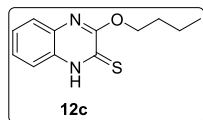


3-Methoxyquinoxaline-2(1H)-thione (12a). Yellow crystals, yield 73%, mp 213–214 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 4.12 (s, 3 H, OCH_3), 7.31–7.66 (m, 4 H, Ar–H), 14.34 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 61.3 (OCH_3), 116.2 (CHAr), 126.3 (CHAr), 126.5 (CHAr), 127.9 (CHAr), 130.6 (Cq), 134.2 (Cq), 151.5 (C = N), 170.3 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : ($M + \text{Na}$) $^+$. 215.2 Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{OS}$ (192.2) C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.23; H, 4.24; N, 14.61; S, 16.73.

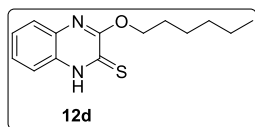


3-Ethoxyquinoxaline-2(1H)-thione (12b). Yellow crystals, yield 85%, mp 202–203 °C. ^1H NMR spectrum (400 MHz, DMSO), δ , ppm (J , Hz): 1.40 (t, 3 H, J = 6.0 Hz, CH_3), 4.45 (q, 2 H, J = 6.0 Hz, OCH_2), 7.36–7.63 (m, 4 H, Ar–H), 14.31 (bs, 1 H, NH). ^{13}C NMR (100.0 MHz, DMSO), δ , ppm: 14.5 (CH_3), 63.8 (OCH_2), 115.9 (CHAr), 126.1 (CHAr), 126.7 (CHAr), 127.8 (CHAr), 130.4 (Cq), 134.0 (Cq), 151.7 (C =

N), 170.0 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 229.2 Anal. Calcd for C₁₀H₁₀N₂OS (206.26) C, 58.23; H, 4.89; N, 13.58; S, 15.54. Found: C, 58.23; H, 4.93; N, 13.64; S, 15.58



3-Butoxyquinoxaline-2(1H)-thione (12c). Yellow crystals, yield 86%, mp 185–186 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J, Hz): 0.96–0.99 (m, 3 H, CH₃), 1.33–1.36 (m, 2 H, CH₂), 1.39–1.42 (m, 2 H, CH₂), 4.03–4.08 (m, 2 H, OCH₂), 7.32–7.61 (m, 4 H, Ar–H), 14.30 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 14.2 (CH₃), 21.4 (CH₂), 28.7 (CH₂), 59.9 (OCH₂), 115.8 (CHAr), 126.2 (CHAr), 126.6 (CHAr), 127.9 (CHAr), 130.6 (Cq), 134.2 (Cq), 151.6 (C = N), 170.2 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 257.3 Anal. Calcd for C₁₂H₁₄N₂OS (234.3) C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.57; H, 6.08; N, 12.02; S, 13.73.



3-Hexyloxyquinoxaline-2(1H)-thione (12d). Yellow crystals, yield 72%, mp 173–174 °C. ¹H NMR spectrum (400 MHz, DMSO), δ , ppm (J, Hz): 0.91–0.94 (m, 3 H, CH₃), 1.29–1.34 (m, 4 H, 2 CH₂), 1.44–1.52 (m, 4 H, 2 CH₂), 4.07–4.11 (m, 2 H, OCH₂), 7.29–7.56 (m, 4 H, Ar–H), 14.33 (bs, 1 H, NH). ¹³C NMR (100.0 MHz, DMSO), δ , ppm: 13.7 (CH₃), 18.5 (CH₂), 24.3 (CH₂), 26.9 (CH₂), 28.6 (CH₂), 59.7 (OCH₂), 115.5 (CHAr), 126.0 (CHAr), 126.4 (CHAr), 127.7 (CHAr), 130.4 (Cq), 134.3 (Cq), 151.4 (C = N), 170.3 (C = S). MS (MALDI, positive mode, matrix DHB) m/z : (M + Na)⁺. 285.3 Anal. Calcd for C₁₄H₁₈N₂OS (262.4) C, 64.09; H, 6.92; N, 10.68; S, 12.22. Found: C, 64.14; H, 6.98; N, 10.72; S, 12.26.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.4c03007>.

The spectroscopic characterization charts of the investigated compounds are provided as electronic Supporting Information (PDF)

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Notes

The authors declare no competing financial interest.

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