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Cyclisation reaction between 3-methylquinoxaline-2-thione and benzaldehydes into 3-benzyl-2-aryl-thieno[2,3-b] quinoxaline promoted by Brønsted acids

*Formation de 3-benzyl-2-arylthieno[2,3-*b*]quinoxaline* via *la cyclisation entre le 3-methylquinoxaline-2-thione et des benzaldehydes induite par des acides de Brønsted*

Besma Saoudi [a,b], Abderrahmane Teniou [b], Adbelmadjid Debache [b,*], Thierry Roisnel [a], Jean-François Soulé [a,*], Henri Doucet [a,*]

[a] *Institut des sciences chimiques de Rennes, UMR 6226 CNRS-Université de Rennes-1 « Organométalliques, matériaux et catalyse », campus de Beaulieu, 263, avenue du Général-Leclerc, 35042 Rennes, France*
[b] *Laboratoire de synthèse des molécules à intérêt biologique, Université Mentouri-Constantine, 25000 Constantine, Algeria*

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ABSTRACT

2,3-Disubstituted thieno[2,3-*b*]quinoxaline derivatives have been synthetized through the condensation of commercially available benzaldehydes with 3-methylquinoxaline-2-thione in EtOH using Brønsted acids, namely sulfuric or hydrochloric acids. A wide range of substituted benzaldehydes has been used, allowing the formation of 3-(substituted)benzyl-2-arylthieno[2,3-*b*]quinoxalines in high yields in only one step.

RÉSUMÉ

Des dérivés thiéno[2,3-*b*]quinoxaline substitués en positions 2 et 3 ont été synthétisés par la condensation de benzaldéhydes avec du 3-méthylquinoxaline-2-thione dans l'EtOH en utilisant des acides de Brønsted, à savoir l'acide sulfurique ou chlorhydrique. Une large gamme de benzaldéhydes substitués a été utilisée, permettant la formation de benzyl-2-arylthieno[2,3-*b*]quinoxalines substituées en position 3 avec des rendements élevés en une seule étape.

1. Introduction

Heterocycle synthesis is a very important field in organic chemistry, because such derivatives play a major role in medicinal chemistry. In addition, such motifs are present in many natural products. Indeed, the discovery of

* Corresponding authors.
E-mail address: jean-francois.soule@univ-rennes1.fr (J.-F. Soulé).

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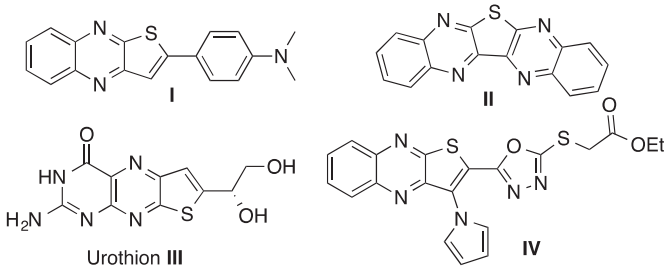


Fig. 1. Relevant thieno[2,3-*b*]quinoxaline structures.

new synthetic methods and/or new heterocyclic compounds has always attracted much attention [1]. Thieno[2,3-*b*]quinoxaline derivatives are polycyclic heterocycles, which have a thiophene ring fused with a quinoxaline motif. Such compounds have found many applications in medicinal as well as in electronic devices (Fig. 1) [2]. For example, *N*,*N*-dimethyl-4-(thieno[2,3-*b*]quinoxalin-2-yl)aniline (**I**) can be used as a fluorescent probe for amyloid-β-fibrils [3], thieno[2,3-*b*:4,5-*b*′]diquinoxaline (**II**) exhibits fluorescence and phosphorescence properties [4], urothion (**III**) is a yellowish pteridine pigment isolated from human urine [5], and ethyl 2-((5-(3-(pyrrol-1-yl)thieno[2,3-*b*]quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)thio)acetate (**IV**) exhibits antimicrobial and fungicide activities [6].

The synthesis of thieno[2,3-*b*]quinoxaline derivatives has been less studied than that of their benzothiophene analogues, and these heterocycles are rather uncommon in the literature [7]. One of the first syntheses of thieno[2,3-*b*]quinoxaline derivatives was achieved from (3-substituted styryl)-2-quinoxalinone in the presence of stoichiometric amounts of phosphorus pentasulfide *via* a thiation, a cyclization and aromatization process [8,9]. 2,3-Disubstitued thieno[2,3-*b*]quinoxaline can be synthesized *via* the condensation of 2-aminoaniline with thiophene-2,3-dione derivatives [10]. More recently, these derivatives were obtained by the action of NaSH on 3-alkynyl-2-chloroquinoxalines [11]. To date, there is no simple and general method for the synthesis of 2,3-disubstitued thieno[2,3-*b*]quinoxaline starting from simple chemicals.

Here, we report on the synthesis of 3-(substituted)-benzyl-2-arylthieno[2,3-*b*]quinoxalines *via* a simple condensation between 3-methylquinoxaline-2-thione and benzaldehydes under acidic conditions.

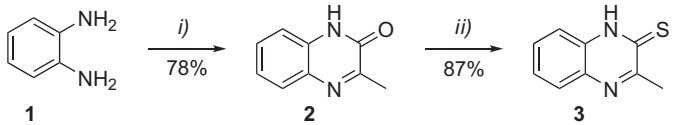
2. Results

We decided to investigate the reactivity of 3-methylquinoxaline-2-thione (**3**) under acidic conditions in the presence of an aldehyde. It is important to note that under basic conditions, 3-methylquinoxaline-2-thione normally reacts at the methyl position *via* alkylation-, or aldolization-type reactions [12–14].

Initially, we prepared the required starting material, i.e. **3**. As described in the literature, **3** could be easily prepared from the condensation of 2-aminoaniline (**1**) with ethyl 2-oxopropanoate under acidic conditions to get 3-methylquinoxalin-2-one (**2**) in 78% yield [15], then **2** is converted to **3** by a thiation in 87% yield, using phosphorus pentasulfide in pyridine under reflux conditions during 6 h (Scheme 1) [16].

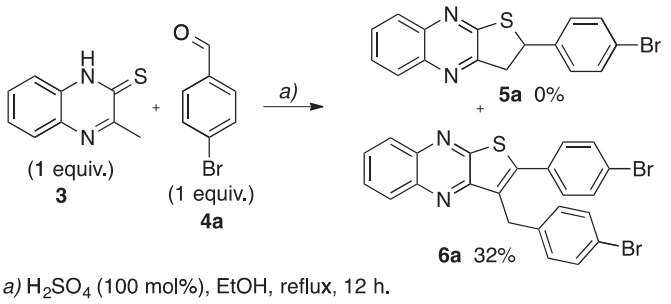
With compound **3** in our hands, we investigated its reactivity in the presence of sulfuric acid and one equivalent of 4-bromobenzaldehyde in EtOH under reflux conditions for 12 h (Scheme 2). Initially, we expected to obtain the 2-substitued-2,3-dihydrothieno[2,3-*b*]quinoxaline derivative **5a**, resulting from the monocondensation between aldehyde **4a** and compound **3**. To our surprise, we obtained the unexpected 2,3-disubstituted thieno[2,3-*b*]quinoxaline **6a**, which results from the condensation of **3** with two molecules of 4-bromobenzaldehyde (**4a**), in 32% yield. We confirmed the structure of **6a** by ^{1}H and ^{13}C NMR studies. In addition, in order to secure unambiguously the structure of the product, the X-ray crystallographic analysis of **6a** was carried out and the result is delineated in Fig. 2.

Then, we investigated the influence of the nature and the amount of the acid for this reaction. We first increased the number of equivalents of aldehyde **4a** to 2 equivalents in the presence of 1 equivalent of sulfuric acid. As a result, the desired product **6a** was obtained in higher yield (48%, Table 1, entry 2). A slight excess of aldehyde (2.2 equivalents) increased again the yield to 52% (Table 1, entry 3). Only trace amounts of the desired product **6a** were observed using only a catalytic amount of sulfuric acid (i.e. 20 mol%) (Table 1, entry 4). This low yield in **6a** was explained by a poor conversion, and large amounts of the starting materials were recovered at the end of the



i) ethyl 2-oxopropanoate (1 equiv.), H_2SO_4 (pH = 2), water, rt, 3 h.
ii) P_2S_5 (1.5 equiv.), pyridine, reflux, 6 h.

Scheme 1. Preparation of 3-methylquinoxaline-2-thione (**3**).



Scheme 2. H_2SO_4-promoted cyclization reaction between 3-methylquinoxaline-2-thione (**3**) and 4-bromobenzaldehyde (**4a**).

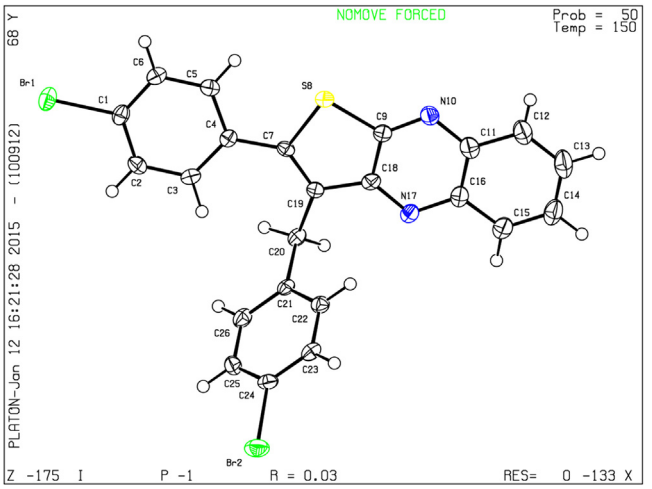
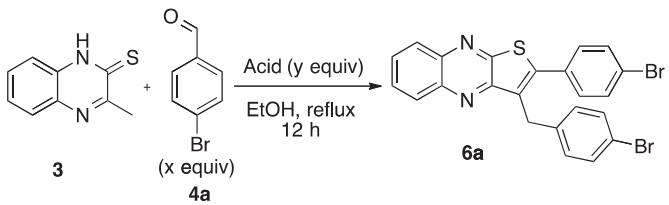


Fig. 2. ORTEP figure for **6a**.

Table 1
Optimization of the reaction conditions for the synthesis of 3-(4-bromobenzyl)-2-(4-bromophenyl)thieno[2,3-*b*]quinoxaline (**6a**).

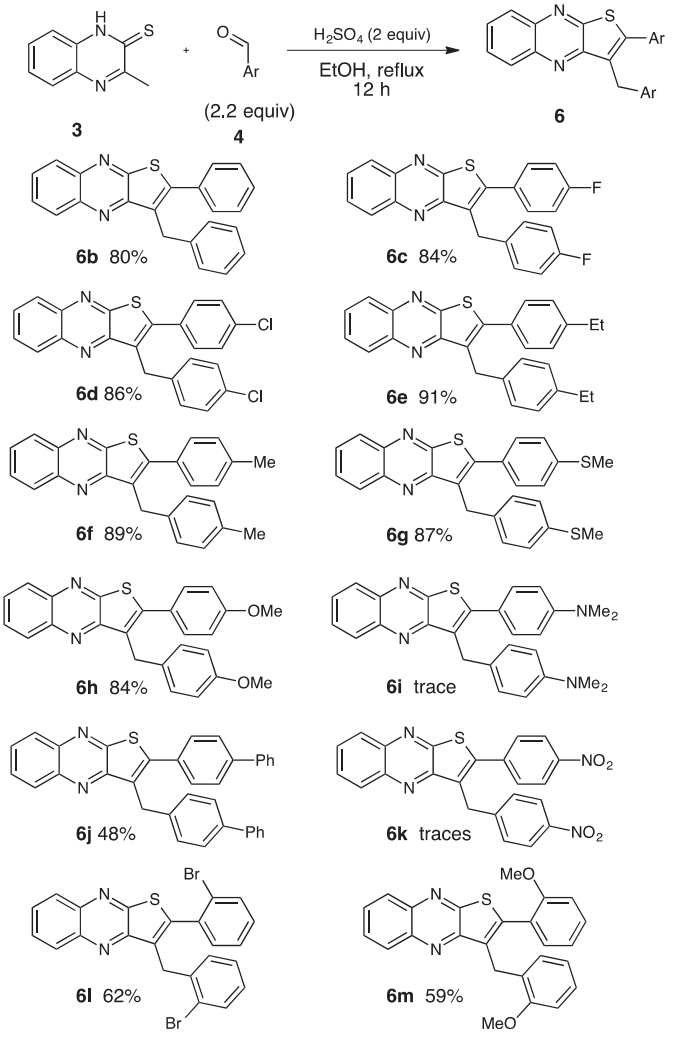


Entry	**4a** (*x* equiv)	Acid (*y* equiv)	**6a** yield (%)[a]
1	1	H_2SO_4 (1)	32
2	2	H_2SO_4 (1)	48
3	2.2	H_2SO_4 (1)	52
4	2.2	H_2SO_4 (0.2)	Trace
5	2.2	H_2SO_4 (1.5)	77
6	2.2	H_2SO_4 (2)	84
7	2.2	H_2SO_4 (2.5)	82
8	2.2	CH_3CO_2H (2)	ND
9	2.2	HCl (2)	79
10	2.2	$FeCl_3.6H_2O$ (2)	ND

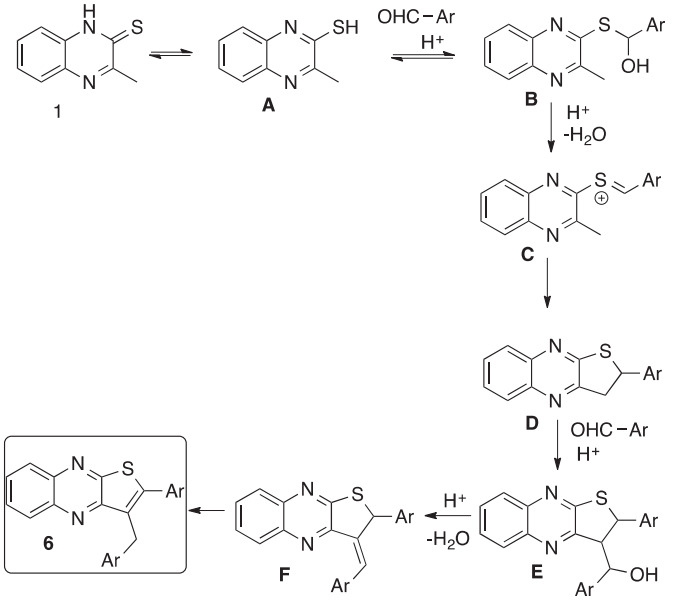
ND: not detected.
[a] Isolated yield.

reaction. Then, we decided to increase the number of equivalents of sulfuric acid. When the reaction was performed in the presence of 1.5 or 2 equivalents of sulfuric acid, thienoquinoxaline **6a** was isolated in 77% and 84% yields, respectively (Table 1, entries 5 and 6) [17]. Larger amounts of sulfuric acid (2.5 equivalents) did not offer any improvement (Table 1, entry 7). Then, we tested other acids for this reaction. The use of 2 equivalents of acetic acid did not afford the desired 2,3-disubstituted thienoquinoxaline **6a** and only the starting materials were recovered at the end of the reaction (Table 1, entry 8). Hydrochloric acid allows the formation of the expected product **6a**, albeit in a slightly lower yield than sulfuric acid (Table 1, entry 9). Iron salts have recently attracted considerable attention as inexpensive and environmentally friendly Lewis acid in a wide range of selective processes in organic synthesis [17,18]. However, no reaction occurred in the presence of this Lewis acid (Table 1, entry 10).

Having determined the best conditions for the formation of 2,3-disubstituted thieno[2,3-*b*]quinoxaline derivatives from 3-methylquinoxaline-2-thione (**3**)—namely, 2.2 equivalents of aldehydes in the presence of 2 equivalents of sulfuric acid in EtOH at reflux during 12 h—we turned our attention to the aldehyde scope for such transformation (Scheme 3). Benzaldehyde also allows the formation of 3-benzyl-2-phenylthieno[2,3-*b*]quinoxaline **6b** in high yield. Other 4-halogenated benzaldehydes such as 4-fluorobenzaldehyde or 4-chlorobenzaldehyde that were reacted with **3** lead to compounds **6c** and **6d** in 84% and 86% yields, respectively. Electron-donating groups at *para*-position such as the methyl, ethyl, methylthio, methoxy ones are also tolerated by the optimized reaction conditions, as the corresponding 2,3-disubstituted thieno[2,3-*b*]quinoxalines **6e**–**6h** were isolated in a range of yields from 84 to 91%. However, with a benzaldehyde bearing a very strong electron-donating group at *para*-position such as the dimethylamino group, only trace amounts of the desired product **6i** were observed. This lack of reactivity could be explained by a poor solubility of the materials and/or of the product. 4-Phenylbenzaldehyde displays a moderate activity, as 2-([1,1′-biphenyl]-4-yl)-3-([1,1′-biphenyl]-4-ylmethyl)thieno[2,3-*b*]quinoxaline (**6j**)



Scheme 3. Scope of the benzaldehydes for H_2SO_4-promoted cyclization with 3-methylquinoxaline-2-thione (**3**).



Scheme 4. H_2SO_4-promoted cyclization of 3-methylquinoxaline-2-thione (**3**) with benzaldehyde: probable sequence leading to 2,3-disubstituted thieno[2,3-*b*]quinoxaline (**6**).

was obtained in only 48% yield. However, 4-nitrobenzaldehyde was completely unreactive under these reaction conditions and the formation of the product **6k** was not detected. The reaction is slightly sensitive to the steric hindrance of the benzaldehyde, as 2-bromobenzaldehyde or 2-anisaldehyde displays lower reactivity than their *para*-substituted homologues. It is also important to note that the reaction was not efficient using aliphatic aldehydes or paraformaldehyde.

We propose a possible sequence for this Brønsted acid-promoted condensation of two equivalent of the benzaldehyde derivative with 3-methylquinoxaline-2-thione (**3**) (Scheme 4). First, the thiol function of intermediate **A**—which is a tautomer of **1**—reacts with a molecule of benzaldehyde under acidic conditions to afford intermediate **B**. Under these acidic conditions, **B** would be dehydrated to allow the formation of thiol-carbenium **C**, which could cyclize to give 2-aryl-2,3-dihydrothieno[2,3-*b*]quinoxaline **D**. Then, a Knoevenagel-type condensation under acidic conditions of the intermediate **D** with another molecule of benzaldehyde leads to compound **F** [19], which is transformed into the desired 2,3-disubstituted thieno[2,3-*b*]quinoxaline (**6**) *via* a rearomatization process.

3. Conclusion

In summary, we developed a new method for the synthesis of new 2,3-disubstituted thieno[2,3-*b*]quinoxalines *via* the condensation of 3-methylquinoxaline-2-thion with a wide range of benzaldehydes. Simple Brønsted acids, such as sulfuric or hydrochloric acid, have been used to promote such a reaction, which was performed in EtOH as a green and renewable solvent. Using this new methodology, we synthetized 11 new compounds, which should present an interest for biological and/or physical properties.

4. Experimental

EtOH (*ethanol*) (95%), H_2SO_4 (98%) were purchased from Acros. Aldehyde compounds were not purified before use. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz) or Bruker GPX (300 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C), coupling constants (J) were reported in hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz or 75 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

General procedure: to a 5-mL oven-dried Schlenk tube, 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol), benzaldehyde (2.2 mmol), H_2SO_4 (106 μL, 2 mmol), EtOH (4 mL) were successively added. The reaction mixture was stirred at 70 °C (oil bath temperature) for 12 h. After cooling the reaction at room temperature and concentration, the crude mixture was poured into ice and the solid was collected by filtration. The crude mixture was purified using flash chromatography (SiO_2, Pentane–Et_2O) and recrystallized in hot EtOH to give the desired product.

4.1. 3-(4-Bromobenzyl)-2-(4-bromophenyl)thieno[2,3-b]quinoxaline (6a)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 4-bromobenzaldehyde (407 mg, 2.2 mmol), the residue was purified

using flash chromatography (SiO_2, pentane–Et_2O 90:10) and recrystallized in hot EtOH to give the desired product **6a** as a yellow solid (84%, 429 mg). mp = 192–197 °C.

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23–8.15 (m, 2H), 7.82–7.77 (m, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 4.40 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.0, 150.8, 146.4, 141.3, 140.6, 138.7, 132.4, 132.2, 131.6, 130.7, 130.1, 129.7, 129.5, 129.2, 129.0, 128.5, 124.1, 120.1, 31.1.

Elemental analysis: calcd (%) $C_{23}H_{14}Br_2N_2S$ for (510.25): C 54.14, H 2.77; found: C 54.37, H 3.01.

MS (EI): calcd for $C_{23}H_{14}Br_2N_2S$ [M+] 510, found: 510.

4.2. 3-(Benzyl)-2-(phenyl)thieno[2,3-b]quinoxaline (6b)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and benzaldehyde (225 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 90:10) and recrystallized in hot EtOH to give the desired product **6b** as a yellow solid (80%, 282 mg). mp = 158–162 °C.

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22–8.16 (m, 2H), 7.77 (t, J = 8.2 Hz, 2H), 7.62–7.59 (m, 2H), 7.49–7.47 (m, 2H), 7.26–7.22 (m, 3H), 4.50 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.3, 151.3, 147.6, 141.3, 140.5, 140.1, 133.7, 129.8, 129.5, 129.3, 129.2, 128.9, 128.9, 128.4, 128.2, 128.0, 127.4, 126.1, 31.7.

Elemental analysis: calcd (%) $C_{23}H_{16}N_2S$ for (352.46): C 78.38, H 4.58; found: C 78.71, H 4.48.

MS (EI): calcd for $C_{23}H_{16}N_2S$ [M+] 352, found: 352.

4.3. 3-(4-Fluorobenzyl)-2-(4-fluorophenyl)thieno[2,3-b]quinoxaline (6c)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 4-fluorobenzaldehyde (236 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 95:5) and recrystallized in hot EtOH to give the desired product **6c** as a yellow solid (84%, 326 mg). mp = 150–154 °C.

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17–8.07 (m, 2H), 7.74–6.64 (m, 2H), 7.47 (dd, J = 5.2 and 8.7 Hz, 2H), 7.15–7.07 (m, 4H), 6.83 (t, J = 8.7 Hz, 2H), 4.35 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4 (d, J = 254.8 Hz), 161.4 (d, J = 245.8 Hz), 156.1, 150.9, 146.5, 141.2, 140.6, 135.5 (d, J = 3.0 Hz), 131.2, 131.1, 129.8 (d, J = 7.6 Hz), 129.7, 129.4, 129.3, 129.1, 128.5, 116.2 (d, J = 16.7 Hz), 115.3 (d, J = 21.3 Hz), 30.9.

Elemental analysis: calcd (%) $C_{23}H_{14}F_2N_2S$ for (388.44): C 71.12, H 3.63; found: C 71.36, H 3.55.

MS (EI): calcd for $C_{23}H_{14}F_2N_2S$ [M+] 388, found: 388.

4.4. 3-(4-Chlorobenzyl)-2-(4-chlorophenyl)thieno[2,3-b]quinoxaline (6d)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 4-chlorobenzaldehyde (309 mg, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 85:15) and recrystallized in hot EtOH to give the desired product **6d** as a yellow solid (86%, 362 mg). mp = 181–185 °C.

^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.24–8.16 (m, 2H), 7.84–7.77 (m, 2H), 7.53–7.46 (m, 4H), 7.23–7.16 (m, 2H), 4.44 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.2, 151.0, 146.6, 141.5, 140.9, 138.5, 136.1, 132.3, 132.2, 130.7, 129.9, 129.7, 129.5, 129.4, 128.8, 128.7, 31.3.

Elemental analysis: calcd (%) $C_{23}H_{14}Cl_2N_2S$ for (421.34): C 65.57, H 3.35; found: C 65.82, H 3.59.

MS (EI): calcd for $C_{23}H_{14}Cl_2N_2S$ [M+] 421, found: 421.

4.5. 3-(4-Ethylbenzyl)-2-(4-ethylphenyl)thieno[2,3-b]quinoxaline (6e)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 4-ethylbenzaldehyde (303 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 85:15) and recrystallized in hot EtOH to give the desired product **6e** as a yellow solid (91%, 372 mg). mp = 152–156 °C.

^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14–8.06 (m, 2H), 7.70–7.65 (m, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 4.40 (s, 2H), 2.65 (q, J = 7.6 Hz, 2H), 2.51 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.4, 151.5, 147.7, 145.9, 141.9, 141.3, 140.4, 131.1, 129.8, 129.3, 129.0, 128.7, 128.5, 128.4, 128.3, 127.9, 31.4, 28.7, 28.4, 15.5, 15.4.

Elemental analysis: calcd (%) $C_{27}H_{24}N_2S$ for (408.56): C 79.38, H 5.92; found: C 79.51, H 6.12.

MS (EI): calcd for $C_{27}H_{24}N_2S$ [M+] 408, found: 408.

4.6. 3-(4-Methylbenzyl)-2-(4-methylphenyl)thieno[2,3-b]quinoxaline (6f)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 4-methylbenzaldehyde (260 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 85:15) and recrystallized in hot EtOH to give the desired product **6f** as a yellow solid (89%, 339 mg). mp = 191–195 °C.

^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.24–8.16 (m, 2H), 7.81–7.74 (m, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 4.47 (s, 2H), 2.45 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.6, 151.7, 147.9, 141.5, 140.7, 139.8, 137.3, 135.7, 131.1, 130.0, 129.9, 129.4, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 31.6, 21.6, 21.2.

Elemental analysis: calcd (%) $C_{25}H_{20}N_2S$ for (380.51): C 78.91, H 5.30; found: C 79.18, H 5.47.

MS (EI): calcd for $C_{25}H_{20}N_2S$ [M+] 380, found: 380.

4.7. 3-(4-(Methylthio)benzyl)-2-(4-(methylthio)phenyl)thieno[2,3-b]quinoxaline (6g)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 4-(methylthio)benzaldehyde (293 μL, 2.2 mmol), the residue

was purified using flash chromatography (SiO_2, pentane–Et_2O 75:25) and recrystallized in hot EtOH to give the desired product **6g** as a yellow solid (87%, 387 mg). mp = 183–187 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.37–8.18 (m, 2H), 7.99–7.79 (m, 2H), 7.62 (d, J = 8.0 Hz), 7.40 (d, J = 8.0 Hz), 7.31–7.23 (m, 4H), 4.55 (s, 2H), 2.67 (s, 3H), 2.55 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.3, 141.4, 141.2, 140.6, 137.1, 135.9, 130.0, 129.8, 129.6, 129.3, 129.1, 128.6, 128.5, 127.1, 126.2, 31.3, 16.2, 15.3.

Elemental analysis: calcd (%) $C_{25}H_{20}N_2S_3$ for (444.63): C 67.53, H 4.53; found: C 67.89, H 4.87.

MS (EI): calcd for $C_{25}H_{20}N_2S_3$ [M+] 444, found: 444.

*4.8. 3-(4-(Methoxy)benzyl)-2-(4-(methoxy)phenyl)thieno[2,3-b]quinoxaline (**6h**)*

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and *p*-anisaldehyde (268 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 80:20) and recrystallized in hot EtOH to give the desired product **6h** as a yellow solid (84%, 347 mg). mp = 161–165 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.24–8.16 (m, 2H), 7.80–7.76 (m, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.45 (s, 2H), 3.90 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.6, 157.9, 156.4, 151.6, 147.4, 141.3, 140.4, 132.2, 130.7, 129.7, 129.4, 129.0, 128.8, 128.5, 128.4, 126.1, 114.4, 113.9, 55.5, 55.2, 30.9.

Elemental analysis: calcd (%) $C_{25}H_{20}N_2O_2S$ for (412.51): C 72.79, H 4.89; found: C 72.81, H 4.77.

MS (EI): calcd for $C_{25}H_{20}N_2O_2S$ [M+] 412, found: 412.

*4.9. 2-([1,1'-Biphenyl]-4-yl)-3-([1,1'-biphenyl]-4-ylmethyl)thieno[2,3-b]quinoxaline (**6j**)*

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and biphenyl-4-carboxaldehyde (401 mg, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 80:20) and recrystallized in hot EtOH to give the desired product **6j** as a yellow solid (48%, 242 mg). mp = 176–180 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.28–8.20 (m, 2H), 7.83–7.79 (m, 2H), 7.77–7.72 (m, 4H), 7.68 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.33 Hz, 2H), 7.54–7.47 (m, 4H), 7.45–7.30 (m, 6H), 4.62 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 151.4, 147.4, 142.3, 141.4, 140.9, 140.6, 140.1, 139.2, 139.1, 132.6, 129.8, 129.2, 129.0, 129.0, 129.0, 128.9, 128.7, 128.5, 127.9, 127.6, 127.2, 127.1, 127.1, 127.0, 31.5.

Elemental analysis: calcd (%) $C_{35}H_{24}N_2S$ for (504.65): C 83.30, H 4.79; found: C 83.57, H 4.71.

MS (EI): calcd for $C_{35}H_{24}N_2S$ [M+] 504, found: 504.

*4.10. 3-(2-bromobenzyl)-2-(2-bromophenyl)thieno[2,3-b]quinoxaline (**6l**)*

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and 2-bromobenzaldehyde (257 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 80:20) and recrystallized in hot EtOH to give the desired product **6l** as a yellow solid (62%, 316 mg). mp = 175–179 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.27–8.20 (m, 2H), 7.84–7.79 (m, 2H), 7.68–7.64 (m, 1H), 7.44 (dd, J = 1.6 and 7.7 Hz, 1H), 7.30–7.24 (m, 3H), 7.08 (dd, J = 2.2 and 7.5 Hz, 1H), 7.03–6.93 (m, 2H), 4.47 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.4, 150.1, 146.7, 141.2, 140.6, 138.5, 134.2, 133.1, 132.4, 131.5, 130.8, 130.6, 130.5, 129.8, 129.5, 129.0, 128.5, 127.6, 127.3, 127.0, 124.5, 123.9, 32.4.

Elemental analysis: calcd (%) $C_{23}H_{14}Br_2N_2S$ for (510.25): C 54.14, H 2.77; found: C 54.33, H 3.02.

MS (EI): calcd for $C_{23}H_{14}Br_2N_2S$ [M+] 510, found: 510.

4.11. 3-(2-methoxybenzyl)-2-(2-methoxyphenyl)thieno[2,3-b]quinoxaline (6m)

Following the general procedure using 3-methylquinoxaline-2-thione (**3**) (176 mg, 1 mmol) and *o*-anisaldehyde (266 μL, 2.2 mmol), the residue was purified using flash chromatography (SiO_2, pentane–Et_2O 80:20) and recrystallized in hot EtOH to give the desired product **6m** as a yellow solid (59%, 243 mg). mp = 181–185 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24–8.17 (m, 2H), 7.79–7.73 (m, 2H), 7.44–7.37 (m, 2H), 7.14–7.08 (m, 2H), 7.04–6.98 (m, 2H), 6.78 (d, J = 8.3 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 4.36 (s, 2H), 3.74 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.4, 157.2, 151.2, 144.7, 141.3, 140.4, 131.6, 130.9, 130.8, 130.0, 129.0, 128.7, 128.5, 128.3, 127.0, 122.8, 120.7, 120.2, 111.4, 110.0, 55.6, 55.3, 26.4.

Elemental analysis: calcd (%) $C_{25}H_{20}N_2O_2S$ for (412.51): C 72.79, H 4.89; found: C 73.06, H 5.08.

MS (EI): calcd for $C_{25}H_{20}N_2O_2S$ [M+] 412, found: 412.

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