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A NEW SYNTHESIS OF NOVEL TRICYCLIC 2(5*H*)-FURANONE HETEROCYCLES FROM 3,4,5-TRICHLORO-2(5*H*)-FURANONE

Jian Ren, Dan-Dan Ma, Yu Sha, Feng Li, and Mao-Sheng Cheng*

The Key Laboratory of Structure-Based Drug Design & Discovery of Ministry of Education, Shenyang Pharmaceutical University, School of Pharmaceutical Engineering, Shenyang, 110016, PR China
*E-mail address: mscheng@syphu.edu.cn

Abstract – A novel class of five-six-six tricyclic 2(5*H*)-furanone heterocycles was synthesized from 3,4,5-trichloro-2(5*H*)-furanone and bifunctional *o*-nucleophiles in a single step. In addition, 2-(chloromethyl)quinoxaline was obtained through this method, and the distinctive formation mechanism of this compound is discussed.

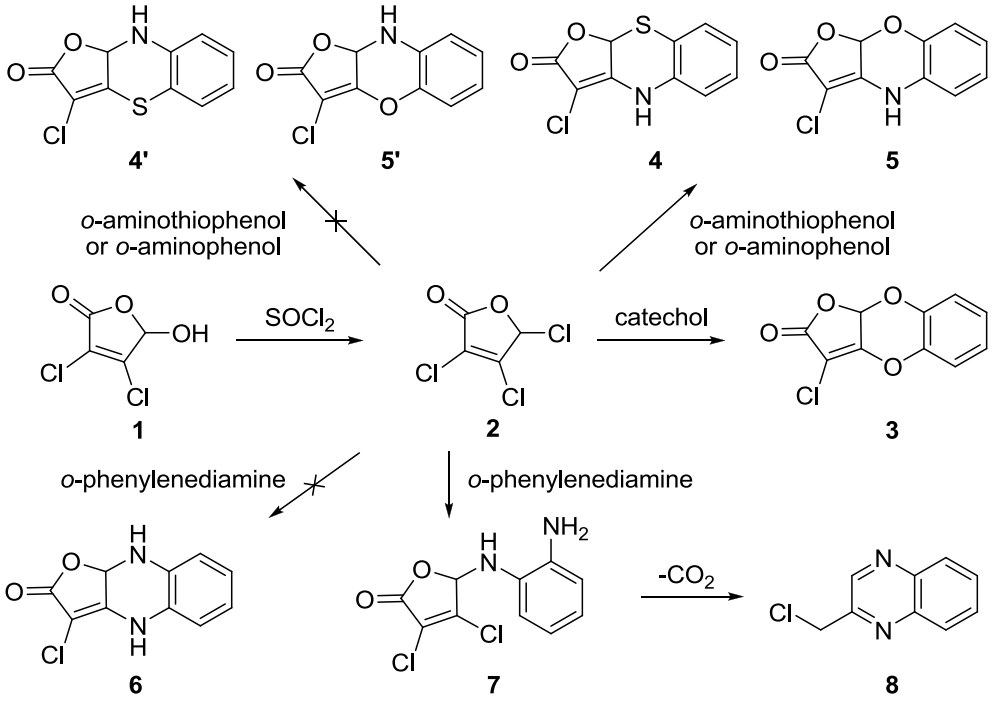
INTRODUCTION

2(5*H*)-Furanone derivatives are a large well-known family of important compounds in medicinal chemistry. A large number of derivatives containing the 2(5*H*)-furanone moiety have been widely used as antitumor,[1] anti-inflammatory,[2] antibacterial,[3] antifungal[4] and antiplatelet[5] agents. Moreover, 2(5*H*)-furanone derivatives have been used in a variety applications in organic synthesis, and there have been many studies reported on their chemistry, synthesis and synthetic uses.[6] The potential applications of the 2(5*H*)-furanone derivatives have attracted considerable attention. 3,4,5-Trichloro-2(5*H*)-furanone is a versatile synthon for the synthesis of different 2(5*H*)-furanone heterocyclic skeletons due to its "pseudo acid chloride" that possesses three potentially reactive chlorides.[7] We report herein on an efficient and general method for the synthesis of a novel class of five-six-six tricyclic 2(5*H*)-furanone heterocycles by reaction of 3,4,5-trichloro-2(5*H*)-furanone with bifunctional *o*-nucleophiles under mild conditions (Scheme 1).

RESULTS AND DISCUSSION

Scheme 1 outlines the synthetic sequences for the preparation of the five-six-six tricyclic 2(5*H*)-furanone heterocycle 3-chlorobenzo[*b*]furo[3,2-*e*][1,4]dioxin-2(9a*H*)-one (**3**) and its analogues **4** and **5**. Initially,

commercially available mucochloric acid (**1**) was used as a starting material. After treatment of **1** with thionyl chloride, the desired important intermediate 3,4,5-trichloro-2(5*H*)-furanone (**2**) was prepared in fair yield. Compound **2** was reacted with catechol and potassium carbonate in dimethylformamide at room temperature for one hour, the corresponding novel 2(5*H*)-furanone heterocyclic compound **3** was obtained in a single step.



Scheme 1

Thus, a convenient method to synthesize novel five-six-six tricyclic 2(5*H*)-furanone heterocycles has been developed. Following this procedure, we attempted to synthesize the 2(5*H*)-furanone heterocyclic analogues **4** and **5** using 3,4,5-trichloro-2(5*H*)-furanone (**2**) as a reaction material. Treatment of **2** with *o*-aminothiophenol offered the desired product 3-chloro-4,9a-dihydro-2*H*-benzo[*b*]furo[3,2-*e*][1,4]-thiazin-2-one (**4**) at a 91% yield at room temperature in less than one hour. In a similar way, 3-chloro-4,9a-dihydro-2*H*-benzo[*b*]furo[3,2-*e*][1,4]oxazin-2-one (**5**) was smoothly cyclized by treatment with **2** and *o*-aminophenol in good yield (88%). By reviewing the relevant literature, we found one report[8] on the preparation of compound **5**, which employed 4-methoxycarbonyloxy-2,3-dichloro-2-buten-4-olide, *o*-aminophenol and CsF as reagents. However, this approach has some drawbacks, such as a tedious workup, unclear yield and a long reaction time (more than 41 hours).

The structures of compounds **4** and **5** were confirmed by their spectral data. In the ^{1}H NMR spectra of compounds **4** and **5**, the methine and NH protons were both signal peaks, and the NH protons of **4** and **5** appeared at δ 11.19 and 11.31 ppm, respectively; these downfield signals indicate that the existence of a nitrogen atom between the phenyl group and the ethylenic bond. In addition, the ^{1}H-^{1}H COSY, NOESY

and HMBC spectrums were also certificated the structures of above two compounds, and the key NOESY and HMBC correlations of **4** and **5** were collected in Figure 1.

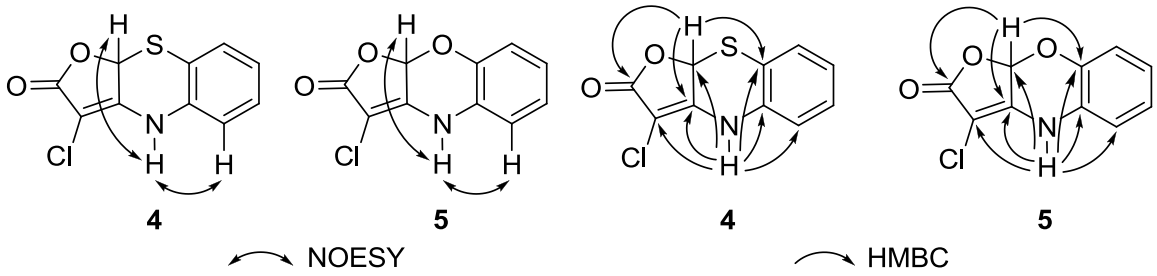


Figure 1. Key NOESY and HMBC correlations of **4** and **5**

Before starting the above two experiments, we supposed that when 3,4,5-trichloro-2(5*H*)-furanone (**2**) reacted with *o*-aminothiophenol or *o*-aminophenol, two isomeric compounds (**4**, **4′** or **5**, **5′**, as noted in Scheme 1) might be generated. Interestingly, in the actual experiments, compounds **4** and **5** were formed as the sole products, and the isomeric compounds **4′** and **5′** were not detected. Therefore, we attempted to use a molecular modeling method[9] to calculate the charge values of the substrate 3,4,5-trichloro-2(5*H*)-furanone in the preliminary analysis of these results. The result of the calculation is shown in Figure 2. As noted in Figure 2, the charge value of the 5-position carbon atom was 0.226, which was slightly higher than that of the 4-position (0.215). This indicated that the electron cloud density of the 5-position was lower than that of the 4-position, and in theory, the 5-position of compound **2** would be attacked first by sulfhydryl or hydroxyl moieties under alkaline conditions.

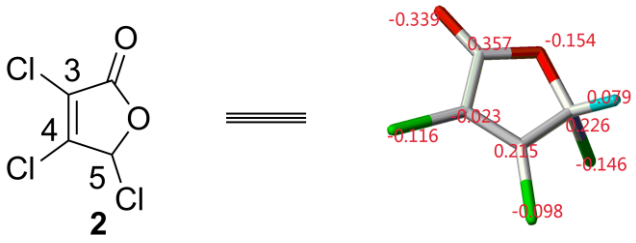
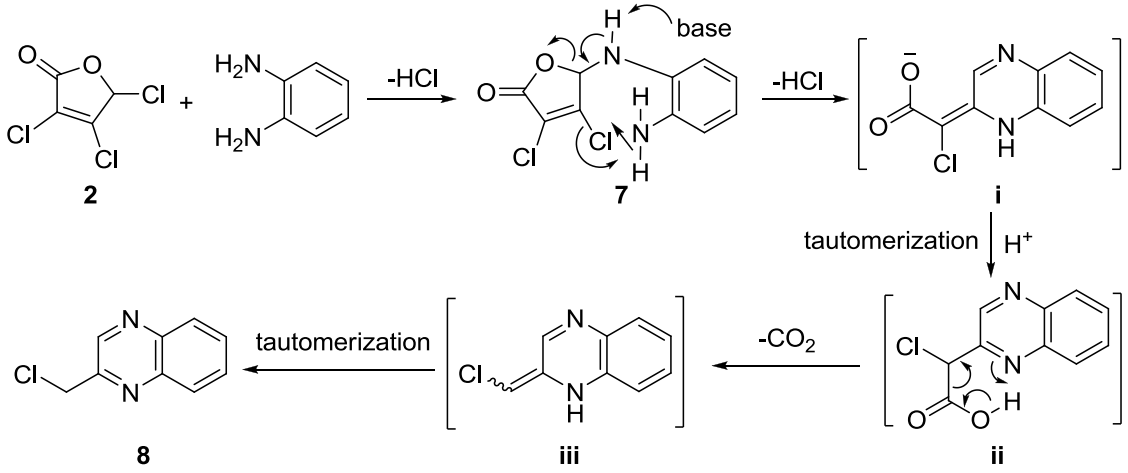


Figure 2

In the following step, we did experiments in an effort to synthesize the tricyclic heterocyclic compound 3-chloro-9,9a-dihydrofuro[2,3-*b*]quinoxalin-2(4*H*)-one (**6**) from 3,4,5-trichloro-2(5*H*)-furanone by reacting with *o*-phenylenediamine (Scheme 1). The desired product **6** was not initially obtained; instead, the decyclized compound **7** was produced. Based on spectral analysis, the structure shown in the Scheme 1 was assigned to compound **7**. Although we attempted to convert **7** to **6** by further reaction under different conditions, such as changing the base, solvent, and reaction time. However, no desired product **6** was generated. After extending the reaction time at room temperature or increasing the temperature, the

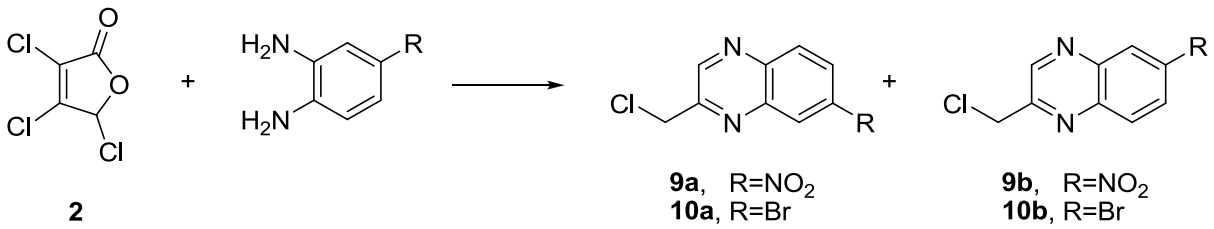
decyclized compound **7** was converted into a surprising product, 2-(chloromethyl)quinoxaline (**8**), which was identified by spectral analysis and further comparison with the reported data.[10] 2-(Chloromethyl)quinoxaline is an available building block for the construction of many bioactive substances[11] with diverse biological activities, including antiarrhythmic, leukotriene biosynthesis inhibitor, phosphodiesterase inhibitor and $GABA_A$ receptor agonist activities. There have only been a few synthetic approaches established previously for the preparation of this compound.[10] Herein, we discovered a simple and practical method for synthesizing this kind of compound.



Scheme 2

Regarding this transformation, the detailed mechanism was not clear at this stage. A possible reaction mechanism accounting for the formation of product **8** is proposed in Scheme 2. The mechanism might involve the following. *o*-Phenylenediamine reacted with 3,4,5-trichloro-2(5*H*)-furanone to generate decyclized compound **7**. The NH moiety of compound **7** was deprotonated with one equivalent base, the furanone ring was opened, and another amino group reacted with 4-position chloride moiety to give **i**. Protonation and tautomerization formed the corresponding "*β*-keto acid" transition state **ii**, which underwent decarboxylation via a six-membered transition state to give **iii**. After further tautomerization, the stable product **8** was obtained.

In order further examine this method, similar reactions were carried out on 4-nitro-1,2-diaminobenzene and 4-bromo-1,2-diaminobenzene.



Scheme 3

From Scheme 3, it can be seen that the reaction of 3,4,5-trichloro-2(5*H*)-furanone (**2**) with 4-nitro-1,2-diaminobenzene or 4-bromo-1,2-diaminobenzene formed the two desired isomers **9a**, **9b** or **10a**, **10b** respectively. The structures of above four compounds were identified by analysis of the ^{1}H and ^{13}C NMR spectroscopic data with the aid of HMBC data. These preliminary results proved that this method could be applied to the synthesis of 2-(chloromethyl)quinoxaline derivatives.

In conclusion, three five-six-six tricyclic 2(5*H*)-furanone heterocyclic compounds and five quinoxaline derivatives were synthesized from 3,4,5-trichloro-2(5*H*)-furanone through a novel method. With respect to *o*-aminothiophenol and *o*-aminophenol, selective reaction with 3,4,5-trichloro-2(5*H*)-furanone generated compound **4** and **5**, and we calculated the charge value of the substrate in the preliminary analysis of this reaction phenomenon. Furthermore, the distinctive reaction mechanism of 2-(chloromethyl)quinoxaline, which was generated by the reaction of 3,4,5-trichloro-2(5*H*)-furanone and *o*-phenylenediamine, was proposed.

EXPERIMENTAL

Melting points were obtained using a Büchi B-540 micro melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded as KBr disks, using Brucker IFS55 spectrometer. All NMR spectra were recorded on a Brucker AM-300 (300 MHz) or AM-600 (600 MHz) spectrometers in dimethyl sulfoxide-d_6 solution at room temperature. The chemical shifts were given in ppm relative to tetramethylsilane as the internal reference standard. The EI mass spectra were performed using an Agilent 6890N-5975i GC-MS. High-resolution mass spectra (HRMS) were determined using a Brucker micrOTOFQ 125.

3,4,5-Trichloro-2(5*H*)-furanone (2): A solution of mucochloric acid (2.0 g, 12.0 mmol) in thionyl chloride (15 mL) was heated under reflux with stirring for 12 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and the crude product was subjected to column chromatography using silica-gel as an absorbent and Petrol/EtOAc = 10:1 as eluent to offer 2.1 g (95%) of **2**. bp 201-202 °C; IR (KBr) *v* max cm^{-1}: 2993, 1809, 1630, 1309, 1226; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 87.20, 123.21, 151.08, 163.26; MS *m*/*z*: 185.9 $[M]^+$, 187.9 $[M+2]^+$, 189.9 $[M+4]^+$, 191.9 $[M+6]^+$.

General procedure for the synthesis of compound 3, 4 and 5: To a stirring suspension of **2** (2.0 g, 10.7 mmol) in DMF (15 mL), the catechol (1.30 g, 11.8 mmol) and K_2CO_3 (1.63 g, 11.8 mmol) was added. After stirring at room temperature for 1 h, ice water was added. The resulting precipitate was collected by filtration and the crude product was subjected to column chromatography using silica-gel as an absorbent and Petrol/EtOAc = 5:1 as eluent to offer 2.04 g **3** (85%). mp 137-138 °C; IR (KBr) *v* max cm^{-1}: 3068, 1789, 1487, 1366, 1110, 762; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.50 (s, 1H), 7.18-7.49 (m, 4H); ^{13}C

NMR (75 MHz, DMSO-d_6): δ 89.67, 96.83, 117.42, 118.90, 124.61, 126.29, 138.52, 140.52, 160.58, 164.39; MS *m*/*z*: 224.0 $[M]^+$, 226.0 $[M+2]^+$; HRMS $[M+Na]^+$ calc for $C_{10}H_5ClNaO_4$: 246.9769, found: 246.9768.

3-Chloro-4,9a-dihydro-2*H*-benzo[*b*]furo[3,2-*e*][1,4]thiazin-2-one (4): This compound was obtained as solid with 2.34 g (91%). mp 201-202 °C; IR (KBr) *v* max cm^{-1}: 3240, 2922, 1743, 1473, 1387, 1058, 752; ^1H NMR (300 MHz, DMSO-d_6): δ 6.44 (s, 1H), 7.02-7.36 (m, 4H), 11.19 (s, 1H); ^1H NMR (600 MHz, DMSO-d_6, deuterium-exchangeable): δ 6.37 (s, 1H), 7.04-7.33 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 70.27, 85.44, 115.16, 118.55, 123.93, 128.35, 129.45, 135.65, 154.01, 167.20; MS *m*/*z*: 239.0 $[M]^+$, 241.0 $[M+2]^+$; HRMS $[M+Na]^+$ calc for $C_{10}H_6ClNNaO_2S$: 261.9700, found: 261.9698.

3-Chloro-4,9a-dihydro-2*H*-benzo[*b*]furo[3,2-*e*][1,4]oxazin-2-one (5): This compound was obtained as solid with 2.11 g (88%). mp 206-207 °C; IR (KBr) *v* max cm^{-1}: 3227, 2910, 1760, 1495, 1399, 1095, 754; ^1H NMR (300 MHz, DMSO-d_6): δ 6.25 (s, 1H), 7.05-7.15 (m, 4H), 11.31 (s, 1H); ^1H NMR (600 MHz, DMSO-d_6, deuterium-exchangeable): δ 6.18 (s, 1H), 7.02-7.12 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 86.18, 91.41, 117.28, 117.92, 124.02, 124.21, 127.36, 140.40, 150.25, 166.20; MS *m*/*z*: 223.0 $[M]^+$, 225.0 $[M+2]^+$; HRMS $[M+Na]^+$ calc for $C_{10}H_6ClNNaO_3$: 245.9928, found: 245.9926.

5-(2-Aminophenylamino)-3,4-dichlorofuran-2(5*H*)-one (7): 3,4,5-Trichloro-2(5*H*)-furanone (2.0 g, 10.7 mmol) in DMF (10 mL), K_2CO_3 (1.63 g, 11.8 mmol) and *o*-phenylenediamine (1.28 g, 11.8 mmol) were added. After the reaction mixture was stirred for 15 min, the solvent was treated with ice/water. The solid deposit was collected by filtration and chromatographed eluting with Petrol/EtOAc = 2:1 to give 2.49 g of **7** (90%). mp 133-134 °C; IR (KBr) *v* max cm^{-1}: 3378, 3239, 2939, 1704, 1502, 1463, 1145, 745; ^1H NMR (300MHz, DMSO-d_6): δ 5.18 (s, 2H), 5.60-5.63 (d, 1H, *J* = 9.0 Hz), 6.51-7.06 (m, 4H), 7.06-7.09 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 82.35, 115.40, 115.67, 119.17, 125.13, 129.13, 130.43, 144.55, 146.49, 161.16; MS *m*/*z*: 258.0 $[M]^+$, 260.0 $[M+2]^+$, 262.0 $[M+4]^+$; HRMS $[M+Na]^+$ calc for $C_{10}H_8Cl_2N_2NaO_2$: 280.9855, found: 280.9856.

General procedure for the synthesis of compound 8, 9a, 9b, 10a and 10b: A mixture of 3,4,5-trichloro-2(5*H*)-furanone (2.0 g, 10.7 mmol), K_2CO_3 (1.63 g, 11.8 mmol) and *o*-phenylenediamine (1.28 g, 11.8 mmol) in DMF (10 mL) was stirred at 60 °C for 0.5 h or at room temperature for 3 h. The solvent was treated with ice/water. After that the solid deposit was collected by filtration and purified by chromatography on a silica-gel column using Petrol/EtOAc = 5:1 to give 1.76 g of **8** (92%). mp 46-47 °C; IR (KBr) *v* max cm^{-1}: 3020, 1637, 1558, 1493, 757; ^1H NMR (300 MHz, DMSO-d_6): δ 5.07 (s, 2H), 7.88-8.15 (m, 4H), 9.10 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 45.07, 129.36, 129.38, 131.10, 131.25, 141.33, 141.67, 146.23, 152.60; MS *m*/*z*: 178.0 $[M]^+$, 180.0 $[M+2]^+$; HRMS $[M+H]^+$ calc for $C_9H_8ClN_2$: 179.0371, found: 179.0365.

2-(Chloromethyl)-7-nitroquinoxaline (9a): This compound was obtained as solid with 0.91 g (38%).

mp 89-90 °C; IR (KBr) *v* max cm^{-1}: 3430, 3045, 1618, 1536, 1347, 1079, 796; ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.13 (s, 2H), 8.33-8.34 (d, 1H, *J* = 9.0 Hz), 8.58-8.60 (dd, 1H, *J* = 9.0 Hz, *J* = 2.5 Hz), 8.93-8.94 (d, 1H, *J* = 2.5 Hz), 9.29 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 44.78, 124.57, 125.45, 131.39, 140.47, 143.91, 148.32, 148.64, 155.85; MS *m*/*z*: 223.1 $[M]^+$, 225.1 $[M+2]^+$; HRMS $[M-H]^-$ calc for $C_9H_5ClN_3O_2$: 222.0076, found: 222.0060.

2-(Chloromethyl)-6-nitroquinoxaline (9b): This compound was obtained as solid with 1.07 g (45%). mp 96-97 °C; IR (KBr) *v* max cm^{-1}: 3431, 3050, 1618, 1530, 1349, 1076, 831; ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.14 (s, 2H), 8.37-8.38 (d, 1H, *J* = 9.0 Hz), 8.58-8.60 (dd, 1H, *J* = 9.0 Hz, *J* = 2.5 Hz), 8.89-8.90 (d, 1H, *J* = 2.5 Hz), 9.30 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 44.30, 123.98, 124.98, 131.06, 139.86, 143.64, 148.11, 149.08, 154.67; MS *m*/*z*: 223.1 $[M]^+$, 225.1 $[M+2]^+$; HRMS $[M-H]^-$ calc for $C_9H_5ClN_3O_2$: 222.0076, found: 222.0081.

2-(Chloromethyl)-7-bromoquinoxaline (10a): This compound was obtained as solid with 0.99 g (36%). mp 62-63 °C; IR (KBr) *v* max cm^{-1}: 3425, 3055, 1582, 1451, 1385, 1091, 750; ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.06 (s, 2H), 8.02-8.05 (m, 2H), 8.37-8.38 (d, 1H, *J* = 2.5 Hz), 9.12 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 44.50, 123.73, 130.85, 131.05, 134.04, 139.82, 141.84, 146.84, 152.76; MS *m*/*z*: 256.0 $[M]^+$, 258.0 $[M+2]^+$, 260.0 $[M+4]^+$; HRMS $[M-H]^-$ calc for $C_9H_5N_2ClBr$: 254.9319, found: 254.9312.

2-(Chloromethyl)-6-bromoquinoxaline (10b): This compound was obtained as solid with 1.15 g (42%). mp 66-67 °C; IR (KBr) *v* max cm^{-1}: 3427, 3045, 1597, 1479, 1362, 1059, 726; ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.04 (s, 2H), 8.00-8.04 (m, 2H), 8.31-8.32 (d, 1H, *J* = 2.5 Hz), 9.10 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 44.43, 123.90, 130.87, 130.95, 133.87, 140.12, 141.57, 146.33, 153.21; MS *m*/*z*: 256.0 $[M]^+$, 258.0 $[M+2]^+$, 260.0 $[M+4]^+$; HRMS $[M-H]^-$ calc for $C_9H_5N_2ClBr$: 254.9319, found: 254.9322.

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