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SYNTHETIC STUDIES OF BIOACTIVE QUINOXALINONES: A FACILE APPROACH TO POTENT EUGLYCEMIC AND HYPOLIPIDEMIC AGENTS

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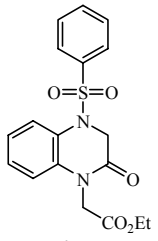
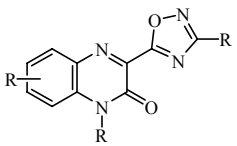
Abstract – Substituted quinoxalin-2-ones have been prepared in high yields in a one-pot reaction in which a 1:1 mixture of 1,2-diaminobenzene and appropriate ethyl 2-bromoalkyl/aryl acetate is subjected to microwave irradiation in presence of DBU at 190 °C for 6 min A possible mechanism is presented.

INTRODUCTION

The quinoxalinone ring is an important pharmacophore found in numerous biologically active compounds. For example, quinoxalinone (**1**) serves as an inhibitor of aldose reductase,[1] while quinoxalinones (**2**) behave as agonists of γ-aminobutyric acid (GABA)/benzodiazepine receptor complex.[2,3] Recently, substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)-ethoxy]phenyl]methylene]thiazolidine-2,4-dione (**3**) have been shown to exhibit remarkable euglycemic and hypolipidemic activities.[4] 2,4-Diones (**3**) that posses an electron donating methyl group at the C-3



1



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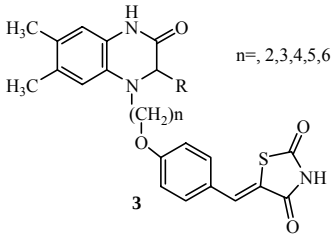


3

position of 1,2,3,4-tetrahydro quinoxalin-2-one decrease glucose level significantly more than those with a phenyl ring at the C-3 position. Quinoxalinones are also used as intermediates in designing quinoxaline derivatives with antimicrobial,[5] antifungal,[6] and anticancer[7] activities. Consequently, a number of combinatorial library synthesis of these class of compounds have been developed.[8-12] In the past several years, microwave (MW) assisted organic reactions have been found to be a rapid and powerful method for developing libraries with high degree of molecular diversities. This new synthetic methodology has

made a major impact on the discovery of new drugs, catalyst, and materials. Herein we report a MW assisted one-pot synthesis of quinoxalinones from certain commerically available 1,2-diaminobenzenes and ethyl 2-bromo-2-alkyl/aryl acetates in the absence of solid support or solvent.

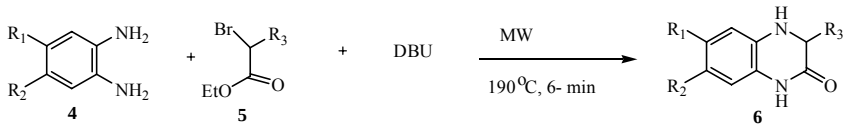
RESULTS AND DISCUSSION

Assuming that a base might help to remove the $-NH_2$ proton of the diamino compound, we irradiated **4a** and **5a** in the presence of several bases for 6 min at 190 ^oC and analyzed the crude reaction mixture by GC/MS analysis. The results, which are shown in Table 1, show that the optimum yield of 3,4-dihydro-3-methyl-1*H*-quinoxalin-2-one (**6a**) was obtained using DBU as base. No further improvement was observed by varying the amount of DBU, temperature or reaction time. In fact when the reaction mixtures were heated longer than 6 min or above 200 ^oC, intractable tarry mixtures were obtained.

Table 1 Influence of Base on Yields of 3,4-Dihydro-3-methyl-1*H*-quinoxalin-2-one (**6a**)

Entry	Base	**6a**, Yields (%)
1	Pyridine	~ 10
2	DMF	~ 5
3	EtN(*i*-prop)$_2$	~15
4	*N*-Methylpyrrolidine	~30
5	*N*-Methylpiperidine	~20
6	K_2CO_3	Trace
7	K_2CO_3 / DMF	Trace
8	Pyridine / *N*-Methylpyrrolidine (1:1)	Trace
9	*N*-Methylpyrrolidine / *N*-Methylpiperidine (1:1)	~30
10	DBU / *N*-Methylpiperidine (1:1)	~70
11	DBU / *N*-Methylpyrrolidine	~40
12	DBU	~90

We next extended this reaction (shown in Scheme 1) to the synthesis of a variety of 3,4-dihydro quinoxalin-2-ones (**6b-l**) by MW irradiation of 1,2-diamino benzenes (**4a,b**) and ethyl 2-bromo-2-alkyl/aryl acetates (**5a-f**) in the presence of DBU at 190 ^{o}C for 6 min in a solvent-free environment. The results shown in Table 2 show that good to excellent yields of **6a-l** were obtained.

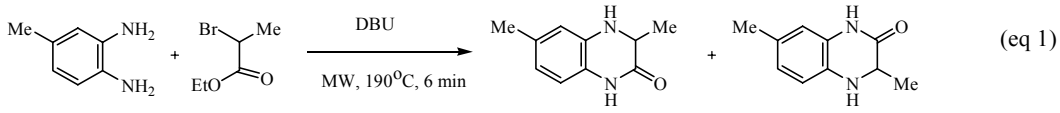


4 5 6

R_1, R_2= H, Me R_3= alkyl or phenyl

Scheme 1

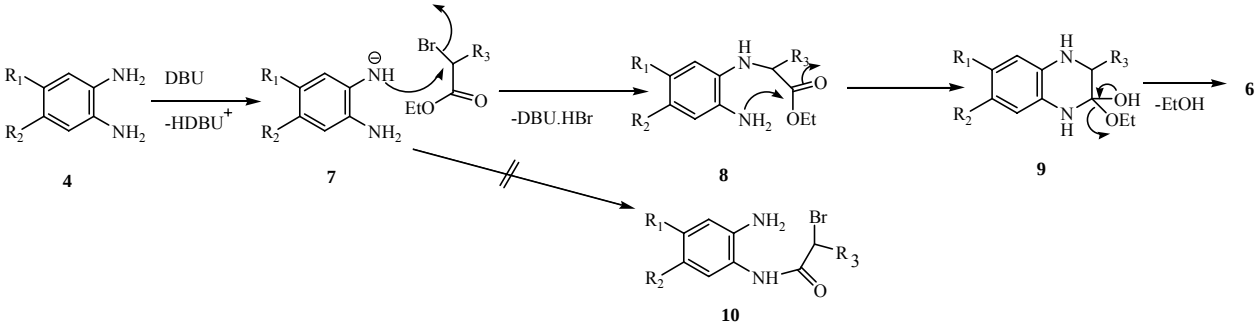
Additionally, when the unsymmetrical diamine (**4c**) was treated with **5a** and DBU (see eq. 1) a 1:1 mixture of the 3,4-dihydro-3,6-dimethyl (**6m**) and 3,4-dihydro-3,7-dimethyl-1*H*-quinoxalin-2-one (**6n**) was obtained in an overall yield of 88% indicating that the reaction is not regioselective. Complete separation of **6m** and **6n** was not possible; however compound (**6m**) was obtained in sufficient purity which allowed its structure to be identified by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy as well as elemental analysis.



(eq 1)

4c **5a** **6m** **6n**

A possible mechanistic pathway (shown in Figure 2) involves the formation of the amidate derivative (**7**) by the reaction of **4** with DBU, which then can attack the bromine-substituted carbon by a S_N2 process to give adducts (**8**) or add to the ester group to give intermediate (**10**). During this process HBr is neutralized by DBU yielding DBU.HBr. When the reaction of **4a** and **5a** was stopped after 3 min and the complex crude reaction mixture was analyzed by GC/MS analysis, unreacted starting material (**4a**) along with intermediate (**8a**) (R_1, R_2 = H, R_3 = Me, M^+ =197 m/z) were observed. There were no traces of the intermediate (**10**). This clearly indicates that the reaction proceeds in former pathway. In the second step, the remaining amino group on **8** adds to the carbonyl carbon of the ester group forming the tetrahedron intermediate **(9)** from which ethyl alcohol is eliminated to give the titled compound. (**6**).



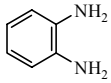
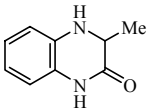
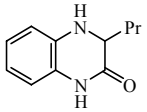
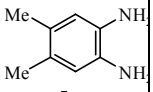
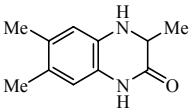
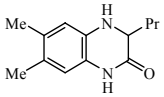
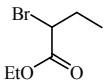
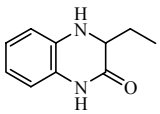
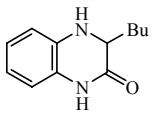
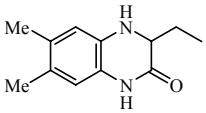
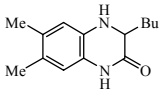
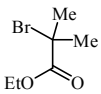
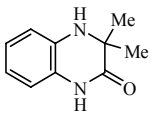
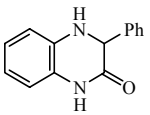
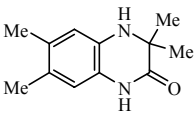
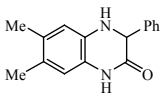
4 7 8 9 6

10

Scheme 2

The elimination of ethyl alcohol was further confirmed by GC/MS analysis of the crude reaction product. In a separate reaction, we found that **4** reacted with **5b** when treated under similar MW conditions, but in the absence of DBU, they failed to react, presumably because free HBr protonated the remaining amino group, thus rendering it non-nucleophilic.

Table 2 Preparation of 3,4-dihydroquinoxalin-2-ones (**6**)

Entry	**4**	**5**	**6**	Yield %	Entry	**4**	**5**	**6**	Yield %
1	 **a**	 **5a**	 **6a**	98%	7	**a**	 **d**	 **g**	92
2	 **b**	**5a**	 **6b**	91%	8	**b**	**d**	 **h**	96
3	**a**	 **5b**	 **6c**	97%	9	**a**	 **e**	 **i**	91
4	**b**	**5b**	 **6d**	93%	10	**b**	**e**	 **j**	87
5	**a**	 **5c**	 **6e**	89%	11	**a**	 **f**	 **k**	70
6	**b**	**5c**	 **6f**	86%	12	**b**	**f**	 **l**	71

In support of this mechanism, the reaction (entries 11 and 12) of ethyl 2-bromo-2-phenylacetate (**5f**) gives the corresponding products (**6k, l)** in lower yields (70, 71%) reflecting a decrease in the electrophilicity of the ester carbonyl group in **8** by the resonance effect of the phenyl group.

In conclusion, we have developed a new high yield solvent free one-pot synthesis of potential biologically important quinoxalin-2-ones (**6a-l**). The 3,3-dimethyl derivative (**6e**) had been previously prepared from an enamine, derived from 2-nitroaniline and an appropriately 2-substituted aldehyde, with CO in the presence of $Pd(dba)_2$, but in only 11% yield.[13] Although the 3-butyl derivative (**6i**) was prepared in a decent 81% yield by the reaction of **4a** with ethyl 2-bromohexanoate and potassium carbonate, the reaction required stirring overnight followed by heating for 3 h at 120 ^oC.[14] Recent reports[15,16] showed that quinoxalin-2-ones can be prepared MW irradiation; however these reactions were supported on soluble polymer. However, the successful use of MW irradiation reported herein requires no solid support or solvent, thus providing another example of a "green" synthesis of biologically important organic molecules.

EXPERIMENTAL

Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker ADVANCE DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. GC/MS experiment was done in HP Gas Chromatograph Electron Ionization Detector (GCD System, G1800C). IR spectra were recorded on a Nicolet MAGNA-IR 560- spectrometer (E. S.P). Elemental analysis was obtained from Southern Methodist University Analytical Service Laboratories. All chemicals were purchased from Fisher Scientific or Aldrich chemicals. Microwave experiment was done in CEM-Discover (From CEM Corporation, POB 200) instrument at 150 W output power.

General Procedure for the Synthesis of Compounds (6a- 6n) via Microwave Irradiation.

A mixture of 1,2-diaminophenol (200 mg, 1.6 mmol) and ethyl alkyl/aryl-2-bromoacetate (1.6 mmol) and DBU (370 mg, 2.5 mmol) was placed in a sealed test tube and irradiate at 190 ^oC for 6 min at 150 W out put. The resulting mixture was dissolved in AcOEt and washed with brine. The AcOEt layer was separated and dried over Na_2SO_4. Evaporation of the solvent afforded crude product mixtures. The solid products were recrystallized from AcOEt-hexane whereas the liquid products were purified by column chromatography using 40% AcOEt-hexane as eluent. The results are shown below.

3,4-Dihydro-3-methyl-1*H*-quinoxalin-2-one (6a): Separated as brownish solid, mp 118-120 ^oC. IR (KBr) $\nu_{c=o}$ 1677 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.48 (d, *J*= 6.4 Hz, 3H, CH_3), 3.88 (br s, 1H, NH), 4.03-4.05 (m, 1H, CH), 6.69 (d, *J* = 7.8 Hz, 1H, aromatic), 6.75-6.79 (m, 2H, aromatic), 6.88-6.91 (m, 1H,

aromatic), 9.13 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 18.3 (CH_3), 52.3 (CH), 114.4 (CH), 115.9 (CH), 119.9 (CH), 124.1 (CH), 126.1 (CH), 133.8 (C), 170.1 (C). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.69; H, 6.21; N, 17.31.

3,4-Dihydro-3,6,7-trimethyl-1*H*-quinoxalin-2-one (6b): Separated as reddish white solid. mp 153-155 ^{o}C. IR (KBr) $\nu_{c=o}$ 1676 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 1.32 (d, J = 6.3 Hz, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.81 (br s, 1H, NH), 5.04 (br s, 1H, NH), 6.53 (s, 1H, aromatic), 6.61 (s, 1H, aromatic), 9.22 (br s, 1H, NH). ^{13}C NMR (acetone-d_6): δ 17.2 (CH_3), 18.4 (CH_3), 18.8 (CH_3), 52.2 (CH), 115.7 (CH), 116.4 (CH), 124.9 (C), 126.4 (C), 130.7 (C), 132.7 (C), 169.1(C). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.46; H, 7.43; N, 14.77.

3-Ethyl-3,4-dihydro-1*H*-quinoxalin-2-one (6c): Separated as colorless gummy liquid. IR ($CHCl_3$) $\nu_{c=o}$ 1678 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3H, CH_3), 1.81-1.91 (m, 2H, CH_2), 3.89 (br s, 1H, NH), 4.00 (br s, 1H, CH), 6.68 (d, J = 7.8 Hz, 1H, aromatic), 6.73-6.77 (m, 2H, aromatic), 6.90 (dd, J = 2.5, 7.8 Hz, 1H, aromatic), 9.2 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 10.0 (CH_3), 25.5 (CH_2) , 57.9 (CH), 114.3 (CH),115.8 (CH), 119.6 (CH), 124.2 (CH), 125.7 (C), 133.4 (C), 169.7 (C). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.16; H, 6.86; N, 15.98.

3-Ethyl-3,4-dihydro- 6,7-dimethyl-1*H*-quinoxalin-2-one (6d): Separated as colorless gummy liquid. IR ($CHCl_3$) $\nu_{c=o}$ 1678 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.04 (t, 3H, CH_3), 1.77-1.87(m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.82 (br s, 1H, NH), 3.86 (br s, 1H, NH), 6.35 (s, 1H, aromatic), 6.55 (s, 1H, aromatic), 9.08 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 10.1 (CH_3), 19.2 (CH_3), 19.7 (CH_3), 25.2 (CH_2), 58.2 (CH), 114.3 (CH), 116.0 (CH), 127.7 (C), 132.1 (C), 132.2 (C), 136.3 (C), 169.7 (C). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.59; H, 8.01; N, 13.73.

3,4-Dihydro-3,3-dimethymethyl-1*H*-quinoxalin-2-one (6e): Separated as brownish solid. mp 135-136 ^{o}C. IR (KBr) $\nu_{c=o}$ 1679 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 1.43 (s, 6H, CH_3 X 2), 3.72 (br s, 1H, NH), 6.68-6.80 (m, 3H, aromatic), 6.91 (dd, J = 3.1, 7.5 Hz, 1H, aromatic), 9.03 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 23.9 (CH_3 X 2), 59.3 (CH), 114.3 (CH), 115.3 (CH), 123.2 (CH), 124.6 (C), 124.9 (C), 127.8 (C), 135.4 (C), 169.9 (C). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.18; H, 6.87; N, 15.91.

3,4-Dihydro-3,3,6,7-tetramethyl-1*H*-quinoxalin-2-one (6f): Separated as brownish solid. mp 78-80 ^{o}C. IR (KBr) $\nu_{c=o}$ 1678 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 1.40 (s, 6H, CH_3 X 2), 2.17 (s, 6H, CH_3 X 2), 3.81 (br s, 1H, NH), 6.38 (s, 1H, aromatic), 6.49 (s, 1H, aromatic), 9.03 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.5 (CH_3 X 2), 19.2 (CH_3), 19.7 (CH_3), 55.9 (CH), 114.3 (CH), 116.5 (CH), 126.8 (C), 132.0 (C), 132.2 (C), 136.3 (C), 169.3 (C). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.55; H, 7.93; N, 13.75.

3,4-Dihydro-3-propyl-1*H*-quinoxalin-2-one (6g): Separated as yellowish gummy liquid. IR ($CHCl_3$) $\nu_{c=o}$ 1678 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 1.31 (t, *J*= 6.9 Hz, 3H, CH_3), 1.48-1.83 (m, 4H, CH_2 X 2), 3.15-3.20 (m, 1H, CH), 3.33 (br s, 1H, NH), 6.68-6.79 (m, 3H, aromatic), 6.83-6.91 (m, 1H, aromatic), 9.01 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 18.9 (CH_2), 34.3 (CH_2), 56.6 (CH), 114.5 (CH), 116.8 (CH), 121.1 (CH), 124.2 (CH), 133.4 (C), 138.4 (C), 170.0 (C). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.50; H, 7.43; N, 14.75.

3,4-Dihydro- 6,7-dimethyl-3-propyl-1*H*-quinoxalin-2-one (6h): Separated as yellowish gummy liquid. IR ($CHCl_3$) $\nu_{c=o}$ 1676 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 0.98 (t, *J*= 7.3 Hz, 3H, CH_3), 1.42-1.76 (m, 4H, CH_2 X 2), 2.36 (s, 6H, CH_3 X 2), 3.15 (br s, 1H, CH), 3.88 (br s, 1H, NH), 6.49 (s, 1H, aromatic), 6.55 (s, 1H, aromatic), 9.06 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 18.9 (CH_3), 19.2(CH_3), 19.7(CH_3), 34.0 (CH_2), 56.8 (CH), 114.3 (CH), 116.0 (CH), 123.6 (C), 127.7 (C), 130.9 (C), 132.1 (C), 169.9 (C). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.55; H, 8.31; N, 12.87.

3-Butyl-3,4-dihydro-1*H*-quinoxalin-2-one (6i): Separated as white solid. mp 90-92^{o}C. IR (KBr) $\nu_{c=o}$ 1678 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.96 (t, *J*= 7.1 Hz, 3H, CH_3), 1.31-1.34 (m, 4H, CH_2), 1.76-1.86 (m, 2H, CH_2), 3.91 (t, *J*= 4.7 Hz, 1H, CH), 3.34 (br s, 1H, NH), 6.64-6.86 (m, 4H, aromatic), 9.5 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 22.9 (CH_2), 27.8 (CH_2), 32.0 (CH_2), 56.8 (CH), 112.9 (CH), 116.8 (CH), 121.1 (CH), 124.2 (CH), 124.6 (CH), 134.4 (C), 169.0 (C). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H,7.90; N, 13.71. Found: C, 70.58; H, 7.96; N, 13.71.

3-Butyl-3,4-dihydro-6,7-dimethyl-1*H*-quinoxalin-2-one (6j): Separated as yellowish solid. mp 85-88 ^{o}C. IR (KBr) $\nu_{c=o}$ 1679 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, *J* = 7.1 Hz, 3H, CH_3), 1.37-1.46 (m, 4H, CH_2), 1.73-1.83 (m, 2H, CH_2), 2.16 (s, 6H, CH_3 X 2), 3.82-3.87 (m, 1H, CH), 6.50 (s, 1H, aromatic), 6.55 (s, 1H, aromatic), 8.88 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 19.2 (CH_3), 19.7 (CH_3), 22.8 (CH_2), 27.9 (CH_2), 31.7 (CH_2), 57.0 (CH), 116.0 (CH), 116.9 (CH), 123.5 (C), 127.7 (C), 130.9 (C), 132.2 (C), 169.8 (C). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.41; H, 8.69; N, 12.06.

3,4-Dihydro- 3-phenyl-1*H*-quinoxalin-2-one (6k): Separated as white solid. mp 195-197 ^{o}C. IR (KBr) $\nu_{c=o}$ 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.10 (br s, 1H, CH), 6.68-6.77 (m, 5H, aromatic), 6.65 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, aromatic), 7.28-7.36 (m, 2H, aromatic), 10.83 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 59.7 (CH), 113.7 (CH), 114.8 (CH), 117.7 (CH), 123.5 (CH), 125.6 (C), 127.5 (CH), 128.8 (CH), 133.8 (C), 140.8 (C), 167.1 (C). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.99; H, 5.44; N, 12.51.

3,4-Dihydro- 6,7-dimethyl-3-phenyl-1*H*-quinoxalin-2-one (6l): Separated as light blue gummy liquid. IR ($CHCl_3$) $\nu_{c=o}$ 1669 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 5.04 (s, 1H, CH), 6.49-6.55 (m, 4H, aromatic), 7.31-7.35 (m, 3H, aromatic), 10.81 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ

18.9 (CH_3), 19.1 (CH_3), 59.3 (CH), 113.1 (CH), 121.5 (C), 121.8 (CH), 127.1 (CH), 127.4 (C), 129.0 (CH), 129.8 (CH), 133.3 (C), 140.1 (C), 168.3 (C). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.18; H, 6.40; N, 11.15.

3,4-Dihydro-3,6-dimethyl-1*H*-quinoxalin-2-one (6m): Separated as a viscous liquid. IR ($CHCl_3$) $\nu_{c=o}$ 1678 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (d, *J*= 6.3 Hz, 3H, -CH_3), 2.25 (s, 3H, -CH_3), 3.80 (br s, 1H, NH), 3.98-4.04 (m, 1H, CH), 6.50-6.62 (m, 2H, aromatic), 6.69-6.71 (m, 1H, aromatic), 9.22 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 18.1 (CH_3), 20.9 (CH_3), 52.3 (CH), 114.5 (CH), 115.7 (CH), 120.5 (CH), 124.5 (C), 129.7 (C), 133.9 (C). 170.5 (C). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C. 68.27; H, 6.91; N, 16.13.

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