

# To Study the Effect of Solvent on the Synthesis of Novel Quinoxaline Derivatives

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## Abstract

Reaction of 2,3-diketoquinoxaline in presence of ferric chloride and hydrazine hydrate gives 2-hydrazino-3-hydroxyquinoxalin (4) which on reaction with various aldehydes in appropriate solvent gives 3-Hydroxy-2-(2'-hydroxy-3-methoxy benzylidene) hydrazine quinoxaline. The structure of compounds 5a-5l has been confirmed by IR and TLC data.

**Keywords:** Quinoxaline; NMDA receptor

## Introduction

Quinoxaline and its analogs constitute the active class of the compound. Further 3-Hydroxy-2-(2'-hydroxy-3-methoxy benzylidene) [1-3] hydrazine quinoxaline are well famed for their antimicrobial activities. In the light of above fact we have synthesized some 3-Hydroxy-2-(2'-hydroxy-3-methoxy benzylidene) [4,5] hydrazine quinoxalines new derivatives incorporating quinoxaline moiety with the hope to possess better antimicrobial activity [4-7].

## Experimental

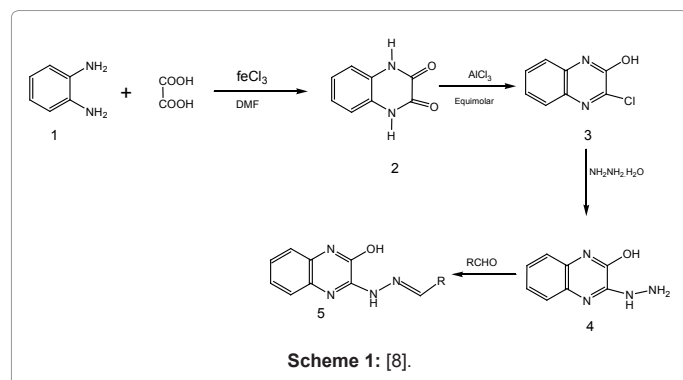
All melting points are determined in an open capillary tube and are found to be uncorrected. IR spectra ( $\text{cm}^{-1}$ ) were recorded on a FTIR-8400 s Shimadzu system. Proton Magnetic Resonance spectra (HNMR) were recorded on Bruker AC-300F NMR spectrometer (300 MHz) using DMSO- $\delta$  6 as solvent and Tetramethyl silane (TMS) as internal standard. All chemical shifts values were recorded as  $\delta$  (ppm). Success of each step was confirmed by TLC during reaction.

### 2,3-Diketoquinoxaline

o-Phenylene diamine (0.25 mole), oxalic acid (0.36 mole) and ferric chloride (0.1 g) and dimethyl formamide (10 ml) were placed in microwave in 800W, and cooled. The solid separated was filtered and washed. m.p.  $<300^\circ\text{C}$ , yield 82%; colorless needle shaped crystals. IR (KBr) 3350, 2928, 1658, 1593, 1028  $\text{cm}^{-1}$ .

### 3-chloroquinoxaline-2-ol

2,3-Diketoquinoxaline (0.01 mole) on treatment with ferric chloride and zinc metal yielded 2-chloro-3-hydroxy quinoxaline.



### 2-Hydrazino 3-hydroxy quinoxaline (4)

The chloro compound (0.015 mole) and hydrazine hydrate (0.02 mole 99%) in ethanol (25 ml) microwave at 800W for few min. to yield 2-hydrazino 3-hydroxy quinoxaline. m.p  $170^\circ\text{C}$ , yield 89%. The product was recrystallized with ethanol to give a pure compound. IR (KBr) 3288  $\text{cm}^{-1}$  and 3186  $\text{cm}^{-1}$  (for NH of  $\text{NH}_2$ ), 1625  $\text{cm}^{-1}$  (C=N Str), 1191  $\text{cm}^{-1}$  (-C-N Str).  $^1\text{H}$  NMR (DMSO- $\delta$ ):  $\delta$  2.52 (s, 3H) 4.23 (br, 2H,  $\text{NH}_2$   $\text{D}_2\text{O}$  exchangeable) 6.2 (br, 1H, NH) 7.77 and 7.87 (d, 2H, quinoxaline ring protons) ppm  $^{13}\text{C}$  NMR showed signals at  $\delta$  127.98 (d, C-5), 129.68 (d, C-7), 127.69 (d, C-8), 140.98 (s, C-9), 141.18 (s, C-10), 147.07 (s, C-2), 152.00 (s, C-3), 127.98 (d, C-5).

### 3-Hydroxy-2-(2'-hydroxy-3-methoxy benzylidene) hydrazine quinoxaline (5)

A mixture of compound 4 (0.01 mole) and benzaldehyde (0.01 mole) in methanol was placed in microwave at 800W. The product separated was isolated and neutralized with sodium bisulphate to get 3-hydroxy-2-(4'-methoxybenzylidene) hydrozino yield 76%; m.p  $184^\circ\text{C}$ .

IR (KBr) 3540  $\text{cm}^{-1}$  (-NH Str), 1623  $\text{cm}^{-1}$  (C=N Str), 1498  $\text{cm}^{-1}$  (-NH def) 1045  $\text{cm}^{-1}$  (- $\text{COCH}_3$ ).  $^1\text{H}$  NMR (DMSO- $\delta$ ): 3.89 (s, 3H, - $\text{OCH}_3$ ), 7.0 and 7.22 (d, 2H, quinoxaline ring protons), 8.4 (s, 1H, N=CH-), and 9.11 (s, 1H, -NH-N) ppm. Above synthesis were performed using different solvent as mentioned in table 1, and found difference in their reaction time and percentage yield. Synthesis of 2-substituted thiazolidione derivatives Catalyzed by  $\text{FeCl}_3$  has been performed as per above method and were shown in table 2.

## Results and Discussion

For the Synthesis of 2,3-Diketoquinoxaline we were used different solvents at same reaction temperature found different reaction time with multiple yields. It can shows that 1,4-dioxane, ethanol and DMF gives highest yield at low reaction time under microwave synthesis.

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Entry	Solvent	T [w]	Time [min]	Yield <sup>b</sup> [%]
1	CH <sub>2</sub> Cl <sub>2</sub>	800	8.0	35.5
2	CH <sub>2</sub> CN	800	1.3	55.3
3	CH <sub>2</sub> OH	800	1.0	67.2
4	1,4-Dioxane	800	3.0	72.8
5	CH <sub>3</sub> CH <sub>2</sub> OH	800	3.0	68.2
6	DMF	800	1.5	80.0
7	DMF	800	2.7	75.9
8	DMF	800	2.0	84.7
9 <sup>c</sup>	DMF	800	1.5	50.2

<sup>a</sup>O-phenylenediamine (1.0 mmole) and benzaldehyde (1.0 mmole), FeCl<sub>3</sub> was 0.1 mmole; the reactions were carried out in the presence of air

<sup>b</sup>Isolated yields

<sup>c</sup>Operated in nitrogen atmosphere

**Table 1:** The effect of solvent and Temperature on the Synthesis of 2,3-Diketoquinoxaline.

Entry	R	Time [h]	Product	Yield <sup>A</sup> [%]	Mp[°c] (lit)
1	C <sub>6</sub> H <sub>5</sub>	1.5	3a	8 3.6	295(298)
2	C <sub>6</sub> H <sub>5</sub>	1.5	3a	63.3 <sup>B</sup>	296
3	C <sub>6</sub> H <sub>5</sub>	1.5	3a	34.2 <sup>C</sup>	294
4	C <sub>6</sub> H <sub>5</sub>	1.5	3a	51.5 <sup>D</sup>	295
5	C <sub>6</sub> H <sub>5</sub>	2.0	3a	66.9 <sup>E</sup>	297
6	2-ClC <sub>6</sub> H <sub>4</sub>	6.5	3b	86.5	230-235(233-234)
7	3-ClC <sub>6</sub> H <sub>4</sub>	1.4	3c	99.5	235-238(238)
8	4-ClC <sub>6</sub> H <sub>4</sub>	1.4	3d	82.5	300-301(302-303)
9	2,Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1.0	3e	86.6	230-235(230-232)
10	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>5</sub>	2.2	3f	99.5	225-228 (226)
11	3-BrC <sub>6</sub> H <sub>4</sub>	0.9	3g	85.7	250-252(252)
12	3-BrC <sub>6</sub> H <sub>4</sub>	3.0	3g	79.8	251
13	3-BrC <sub>6</sub> H <sub>4</sub>	5.0	3g	77.3	252
14	3-BrC <sub>6</sub> H <sub>4</sub>	0.9	3g	70.4	253
15	3-BrC <sub>6</sub> H <sub>4</sub>	0.9	3g	80.2 <sup>I</sup>	252
16	4-BrC <sub>6</sub> H <sub>4</sub>	1.0	3h	81.4	296-300 (299)
17	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.2	3i	83.7	203-205 (201)
18	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.2	3j	87.3	297-301(298-300)
19	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.2	3j	64.0 <sup>D</sup>	299
20	2-OHC <sub>6</sub> H <sub>4</sub>	4.5	3k	91.7	235-238(236-237)
21	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1.7	3l	97.5 <sup>D</sup>	266-271(270)
22	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1.7	3l	51.8	272
23	4-(Me <sub>2</sub> )NC <sub>6</sub> H <sub>4</sub>	2.7	3m	80.7	232-237(233-236)
24	2-Furyl	1.4	3n	76.8	310-315(310-312)
25	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	3.0		trace	313
26	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	3.0		Treace	315

<sup>A</sup>Isolated yield

<sup>B</sup>FeCl<sub>3</sub> as a catalyst

<sup>C</sup>Stirred without ultrasound

<sup>E</sup>O-phenylenediamine (1.0 mmol) and benzaldehyde (2.0 mmole)

<sup>F</sup>First recycled FeCl<sub>3</sub> was use

<sup>G</sup>Second recycled FeCl<sub>3</sub> was used

<sup>H</sup>Ultrasonic cleaner with a frequency of 25 KHz

<sup>I</sup>Ultrasonic cleaner with a frequency of 59 KHz

**Table 2:** The Synthesis of 2-substituted thiazolidione derivatives Catalyzed by FeCl<sub>3</sub> under Ultrasound.

The chemical synthesis initiate with the reaction of *o*-Phenylenediamine 1 and Oxalic acid were mixed in ferric chloride and dimethyl formamide to yield 2,3-Diketoquinoxaline 2, which on treatment with ferric chloride and zinc metal yielded 2-chloro-3-methyl quinoxaline (3). The chloro compound and hydrazine hydrate were placed in microwave for few min. to yield 2-hydrazino 3-hydroxy quinoxaline (4). A mixture of compound 4 and different aromatic aldehydes in methanol placed in microwave to give 3-hydroxy-2-(arylidene hydrazine) quinoxaline 5. The structure of all the newly quinoxaline derivatives were confirmed

on the basis of their spectral and analytical data. The IR spectrum of compound 4 showed a sharp doublet at 3286 cm<sup>-1</sup> and 3188 cm<sup>-1</sup> due to the NH stretch of NH<sub>2</sub>. On condensation with carbonyl compounds, these bands disappear and a band at 3298 cm<sup>-1</sup> is observed due to NH stretch of NH=N group. The 1H NMR spectrum of compound 4 showed a broad signal at δ 4.25 due to NH<sub>2</sub> protons and at δ 6.5 the characteristics of NH proton. The compound on condensation with carbonyl compounds the hydrazone formed shows the disappearance of NH<sub>2</sub> proton signals, while that of NH proton signal is shifted up field

at  $\delta$  9.12 as a result of de shielding effect of CH=N- group. The proton of azomethane group is lead to a sharp singlet at  $\delta$  8.4. The multiplet signals at  $\delta$  6.9-8.4 are the characteristics of the aromatic protons. A sharp signal appears at  $\delta$  3.93, the characteristics of the protons of -OCH<sub>3</sub>. In case of 2-p-anisyl-3-(3'-hydroxyquinoxalin-2'-yl-amino) 4 thiazolidinone gave a sharp signal at  $\delta$  3.69 the characteristics of the proton of -CH<sub>2</sub> group of 4-thiazolidinone ring. The NMR spectrum of 1-N-(3'-hydroxyquinoxalin-2'-yl-amino) 4- methoxybenzylidene-3-chloro-2-azetidinone gave two doublets at  $\delta$  4.67 and  $\delta$  3.75 due to the two hydrogen atoms on C<sub>3</sub> and C<sub>4</sub> carbon atom respectively.

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