

## Synthesis of physiologically important quinoxaline derivatives using conventional method and microwave irradiation

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Quinoxaline derivatives are pharmacologically active and are very useful. A number of quinoxaline derivatives have been synthesized by the reaction of 2-chloroquinoxaline with various substituted amines in the presence of pyridine. The reactions have been carried out following conventional procedure and also under microwave irradiation.

**Keywords:** Synthesis, Quinoxaline, Microwave irradiation

Quinoxaline derivatives play a vital role in biological fields. Many of the anti-malarial<sup>1</sup>, antifungal<sup>2</sup>, antibacterial<sup>3</sup>, anti-HIV, antidiabetic, anti-viral<sup>4</sup> drugs contain quinoxaline nucleus. A slight change in the substituent (s) attached to the quinoxaline derivative remarkably affect biological activity of the drugs. The use of microwave irradiation<sup>5</sup> in chemical synthesis is eco-friendly and free from pollution hazard. The microwave assisted reactions are rapid, safe, high yielding<sup>6</sup> and superior to conventional methods. The condensation of 2-chloroquinoxaline with various substituted amines was carried out by both conventional and microwave methods. In conventional method it took 5-6 days whereas under microwave irradiation, it took only 10-20 min for completion of the reaction.

### Experimental Procedure

Melting points were determined in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel 'G' coated glass plates. IR spectra were recorded in KBr discs on a Nexus FT-IR spectrometer. <sup>1</sup>H NMR spectra were recorded on a Bruker QRX-300 at 500MHz using TMS as an internal standard. GC-MS spectra were taken on a Perkin-Elmer Clarus 500. Microwave assisted reactions were carried out in a Samsung M197 DL

domestic microwave oven. Organic solvents used were of high purity MeOH (Merck), ethyl acetate (Qualigens), CHCl<sub>3</sub>, acetone (Rankem), petroleum ether (Merck) and were used as such without further purification. Organic chemicals, silicagel 60-120 mesh (Qualigens), 2-chloroquinoxaline (Aldrich), imidazole (Merck), tryptamine (Aldrich), pyrimidine (Aldrich), thiosemicarbazide (Merck), sulphacetamide (Rankem), pyridine(Rankem), phenylhydrazine(Qualigens) were used as such.

### Synthesis of 1-(Quinoxalin-2-yl)thiosemicarbazide (3a)

#### Conventional method

2-Chloroquinoxaline (1 mmol, 100 mg) and thiosemicarbazide(1 mmol, 56 mg) were dissolved in MeOH and 2-3 drops of pyridine were added. The resultant mixture was kept at room temperature at 30°C for 5-6 days and then distilled under vacuum. The crude product obtained was then purified by column chromatography over silica gel. Final product **3a** was characterized by <sup>1</sup>H NMR, IR, GC-MS and other physical data.

#### Microwave method

A mixture of 2-chloroquinoxaline (1 mmol, 100 mg) and thiosemicarbazide (1 mmol, 56 mg) was taken in a RB flask and dissolved in 10 mL MeOH. To the clear solution was added 2-3 drops of pyridine and then subjected to microwave irradiation (300W, 10 min). The progress of the reaction was monitored using TLC. On completion of the reaction, the solvent was distilled off and the crude product was washed with diethyl ether to get the final pure product **3a** and was then fully characterized by spectral and other analytical data.

The other compounds (**3b-c** and **5**) were also synthesized using microwave irradiation and characterized by their spectral and other physical constants. It is clear from the above that microwave irradiation led to the formation of product **3a** in short time(10 min) as compared to conventional method (5-6 days). The percentage yield using microwave irradiation is high (90%) as compared to conventional method (30%).

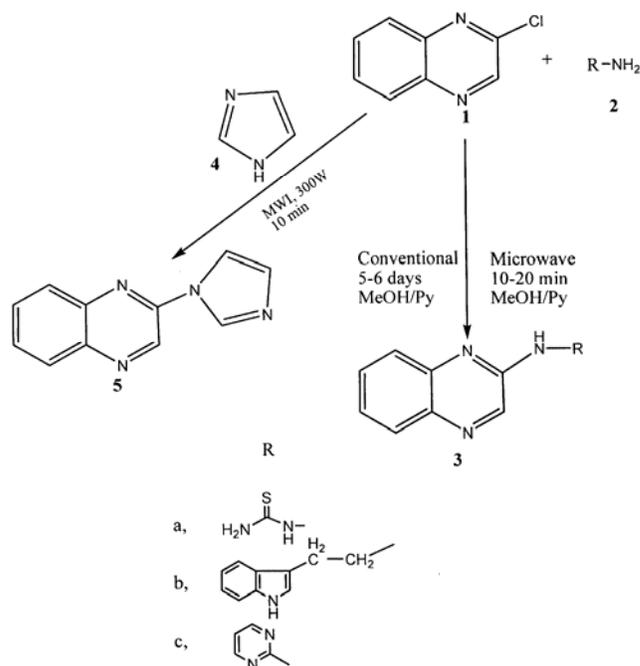
### Results and Discussion

The reaction of 2-chloroquinoxaline **1** with hydrazine carbothioamide **2a** in methanol and catalytic amount of

pyridine under microwave irradiation afforded 1-(quinoxalin-2-yl)thiosemi-carbazide **3a** in quantitative yield (Scheme 1). It is noteworthy that the reaction was completed within 10 min. When the same reaction was performed under conventional heating method in MeOH/Py it resulted in the formation of **3a** in low yields and required 5-6 days. So, MORE (Microwave induced Organic Reaction Enhancement) technique has a clear advantage over the conventional mode. The IR spectrum of **3a** showed absorptions at 3468 (N-H stretch) and at 3482 and 3282  $\text{cm}^{-1}$  ( $\text{NH}_2$  group).  $^1\text{H}$  NMR of **3a** supported the formation of the desired product. Mass spectrum of **3a** showed molecular ion peak at  $m/z$  219. When 2-chloroquinoxaline **1** was condensed with 1H-Indole-3-ethanamine **2b** under microwave irradiation, product N-(2-(1H-indol-3-yl)ethyl)quinoxalin-2-amine **3b** was obtained in good yield (Table 1) which had been fully characterized by IR,  $^1\text{H}$  NMR and mass spectral data.  $^1\text{H}$  NMR showed broad singlet at  $\delta$  10.98 due to 2 NH protons, which were  $\text{D}_2\text{O}$  exchangeable. Signals of aromatic protons in the region 6.99-7.57  $\delta$  (10 protons), a triplet at  $\delta$  3.04 due to 2 protons of  $-\text{CH}_2-$  group and a 2<sup>nd</sup> triplet at  $\delta$  2.99 due to 2 protons of another  $-\text{CH}_2-$  group were observed. Mass spectrum showed molecular ion peak at  $m/z$  288. When the same reaction was carried out under conventional heating conditions, product **3b** was obtained in very low yield and took 5-6 days. Similarly compounds **3c**, i.e., 2-(1H-imidazol-1-yl)quinoxaline and **5**, i.e., N-(pyrimidin-2-

yl)quinoxaline-2-amine were synthesized under microwave irradiation and characterized by IR,  $^1\text{H}$  NMR and mass spectral data (Table 1).

Thus, quinoxaline derivatives can be synthesized by the reaction of 2-chloroquinoxaline with various substituted amines in the presence of pyridine under microwave irradiation. The used microwave



Scheme 1

Table 1—Characteristic data of compounds **3a-c** and **5**

Compound	M.P $^{\circ}\text{C}$	Yield(%)		IR ( $\text{cm}^{-1}$ ), $^1\text{H}$ NMR ( $\delta$ ), GC-MS $m/z$
		Conventional	Microwave	
<b>3a</b> ( $\text{C}_{18}\text{H}_{16}\text{N}_4$ )	160	30	90	IR: 3408(N-H), 3482 & 3282 ( $\text{NH}_2$ ), 1656 ( $-\overset{\text{S}}{\text{C}}-\text{NH}_2$ ), 1617, 1569 & 1526 (Ar,C=C); $^1\text{H}$ NMR : 9.12(s, 1H, Ar), 8.61-8.57(d, 2H, NH-NH, exchangeable with $\text{D}_2\text{O}$ ), 8.13- 8.12(d, 2H, $\text{NH}_2$ , exch with $\text{D}_2\text{O}$ ), 7.79-7.68 (2 triplets, 4H, Ar); GC-MS: $\text{M}^+$ peak at 219(1%), 203( $\text{M}^+-\text{NH}_2$ ; 17%), 202( $\text{C}_{18}\text{H}_{16}\text{N}_4$ , 100%), 144( $\text{C}_{18}\text{H}_{16}\text{N}_4$ , 57%)
<b>3b</b> ( $\text{C}_{18}\text{H}_{16}\text{N}_4$ )	120	25	92	IR: 3290(N-H), 3026(Ar C-H), 1596,1501(Ar); $^1\text{H}$ NMR : 10.98(s, 2H, NH, exch with $\text{D}_2\text{O}$ ), 7.57- 7.55 (d, 2H, Ar), 7.38-7.36(d, 2H, Ar), 7.23(s, 2H, Ar), 7.11- 7.08(t, 2H, J=7.5 Hz, Ar), 7.02-6.99(t, 2H, J=7.5 Hz, Ar), 3.05- 3.04(t, 2H, $\text{CH}_2$ ), 3.00- 2.99(t, 2H, $\text{CH}_2$ ); GC-MS: $\text{M}^+$ peak at 288
<b>3c</b> ( $\text{C}_{12}\text{H}_9\text{N}_5$ )	110	30	89	IR: 3170(N-H),3065 (Ar C-H),1647,1560, 1479 (Ar C=C); $^1\text{H}$ NMR : 11.80(s, 1H, NH, exch with $\text{D}_2\text{O}$ ), 7.91- 7.90 (d, 2H, Ar), 7.55(t, 3H, Ar), 7.30(d,1H, J=7.5 Hz, Ar), 7.01-7.00(d, 1H, J=7.5 Hz, Ar), 6.36 (s,1H, Ar); GC-MS: $\text{M}^+$ peak at 223 (7%), 79( $\text{C}_{12}\text{H}_9\text{N}_5$ , 8%)
<b>5</b> ( $\text{C}_{11}\text{H}_8\text{N}_4$ )	100	33	87	IR: 3052(Ar C-H),1622, 1570,1495(Ar C=N); $^1\text{H}$ ( $\text{C}_{11}\text{H}_8\text{N}_4$ ) NMR : 9.55(s,1H, Ar),8.84(s, 1H, Ar), 8.21(s, 1H, Ar), 8.17- 8.15(d, 1H, J=8 Hz, Ar),8.08- 8.06(d,1H, J=8 Hz, Ar), 7.94-7.91 (t, 1H, J=7.5 Hz, Ar),7.87-7.84(t, 1H, J=7.5 Hz, Ar), 7.25(s, 1H, Ar); GC-MS: $\text{M}^+$ peak at 196(10%)

irradiation facilitate the formation of products in short time as compared to conventional method. The percentage yield using microwave irradiation is high (>87%) as compared to conventional method(33%). The product formation was fast, eco-friendly, cheaper, high yielding and easy to handle in comparison with conventional method.

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