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# Microwave assisted synthesis of 2-(1-alkyl/aralkyl-*1H*-benzimidazole-2-yl)-quinoxaline derivatives

**K. Srinivas[1] and P. K. Dubey[2]**

[1]*Department of Chemistry, GITAM Institute of Technology, GITAM University, Rushikonda, Visakhapatnam (A.P.), India*
[2]*Department of Chemistry, College of Engineering, Jawaharlal Nehru Technological University, Hyderabad, Kukatpally, Hyderabad (A.P.), India*

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**ABSTRACT**

*Synthesis of the 2-(1-alkyl/aralkyl-1h-benzimidazole-2-yl)-quinoxaline derivatives* ***(3)*** *by treatment of N-alkyl/aralkyl-2-α-bromoacetylbenzimidazole* ***(1)*** *with substituted o-Phenylene diamine* ***(2)*** *under microwave irradiation technique is described.*

**Keywords:** o-Phenylenediamine, Bromine, Microwave Irradiation.

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## INTRODUCTION

Several microwave assisted organic reactions proceed under mild reaction conditions at much enhanced reaction rates relative to thermal reactions [1]. Hence the decomposition of reactants and/or products is diminished in these reactions leading to enhanced yields. Microwave irradiation has been used to effect organic reactions such as pericyclic [2], cyclisation [3], aromatic substitution [4], oxidation [5], alkylation [6], decarboxylation [7], radical reactions [8], condensation [9], peptide synthesis reactions and also in various reactions [10].

Among the various classes of nitrogen containing heterocyclic compounds, benzimidazoles and quinoxalines have been shown [11] to exhibit a wide range of biological and pharmacological properties. The benzimidazole derivatives have commercial application in veterinary medicine as anthelmintic agents [12] and in such diverse human therapeutic areas [13-16] as anti-ulcerous, anti-hypertensive, anti-viral, anti-fungal, anti-cancerous and anti-histaminic agents. They also find application as molecular probes [17] to name just a few of their uses. Quinoxaline ring is a part of a number of anti-biotics such as echinomycin, leromycin, and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors [18]. Incorporating two biologically active moieties - benzimidazole and quinoxaline - in a single molecule may lead to interesting pharmacological properties.

In this study, we have employed microwave irradiation for the synthesis of title compounds. This work assumes importance, in view of the fact that benzimidazoles and their derivatives display a number of important biological activities such as local anesthetic, antipyretic and antihistaminic and hence possess great chemotherapeutic potential.

## MATERIALS AND METHODS

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. TLC analysis was performed on silica gel-G and spotting was done using iodine or UV light. IR spectra were recorded on Perkin – Elmer model 446 instrument in KBr phase. $^1$H NMR was recorded in $CDCl_3$/DMSO-$d_6$ using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on LCMS spectrometer. Experiments under microwave irradiation are carried out by using Kenstar domestic microwave oven (MOD: OM- 34 ECR). The required starting materials N-alkyl/aralkyl-2-α-bromoacetyl benzimidazole **(1**) was synthesized according to the literature method reported earlier [20].

**Preparation of 3 (General procedure):**
A mixture of **1** (5 mmol) and **2** (5 mmol) in dry DMF (1 ml) was taken in an 50 ml Erlenmeyer Flask and subjected to Microwave irradiation at 50% for the specified time as indicated in Table-I. The completion of reaction was monitored by TLC. The reaction mixture was cooled to RT and poured into ice-cold water (30 mL). The mixture was neutralized with saturated solution of $NaHCO_3$. The separated product was filtered, washed with chilled water, further solid was dissolved in methanol/chloroform, dried over anh.$Na_2SO_4$, filtered, concentrated the solvent under reduced pressure to give crude product, which was purified by recrystallisation from diethyl ether and n-pentane to obtain pure **3** (table-I).

**Spectral data:**
**2-(1-Methyl-1H-benzimidazole-2yl)quinoxaline** (**3a):** R=$CH_3$, $R^1$=H; Its $^1$H-NMR (DMSO-d6/TMS) showed signals at δ 4.4(s, 3H, -C**H**$_3$), 7.3-8.3 (m, 8H, **aryl** protons), 9.8(s, $^1$H, -C**H**=N in quinoxaline); $M^+$+1: 261.

**2-(1-Ethyl-1H-benzimidazole-2yl)quinoxaline** (**3b):** R=$C_2H_5$, $R^1$=H, Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 1.5(t, 3H, $CH_3$), 4.9(q, 2H, -C**H**$_2$), 7.3-8.2(m, 8H, **aryl** protons), 9.8 (s, 1H, -C**H**=N in quinoxaline). $M^+$+1:276.

**2-(1-Benzyl-1H-benzimidazole-2yl)quinoxaline** (**3c):** R=$CH_2$-Ph, $R^1$=H, Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 6.3( s, 2H, -C**H**$_2$), 7.2-8.1(m, 13H, **aryl** protons), 9.8 (s, 1H, -C**H**=N in quinoxaline). $M^+$+1: 337.

**6-Bromo-2-(1-methyl-1H-benzimidazole-2yl)quinoxaline** (**3d):** R=$CH_3$, $R^1$=Br, Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 4.4( s, 3H, -C**H**$_3$),7.3-8.3(m, 7H, **aryl** protons), 9.8 (s, 1H, -C**H**=N in quinoxaline). $M^+$+1: 279.

**6-Fluro-2-(1-methyl-1H-benzimidazole-2yl)quinoxaline 3e**: R=$CH_3$, $R^1$=F; Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 4.4 (s, 3H, -C**H**$_3$), 7.3-8.3 (m, 7H, **aryl protons**), 9.8 (s, 1H, -C**H**=N in quinoxaline). M $^+$+1: 279.

**6-Bromo-2-(1-ethyl-1H-benzimidazole-2yl)quinoxaline (3f)**: R=$C_2H_5$, $R^1$=Br; Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 1.5 (t, 3H, -C**H**$_3$), 4.9 (q, 2H, -C**H**$_2$), 7.3-8.3 (m, 7H, **aryl protons**), 9.8 (s, 1H, -C**H**=N in quinoxaline); M $^+$+1: 354.

**6-Fluro-2-(1-ethyl-1H-benzimidazole-2yl)quinoxaline (3g)**: R=$C_2H_5$, $R^1$=F; Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 4.4 (s, 3H, -C**H**$_3$), 7.3-8.3 (m, 8H, **aryl protons**), 9.8 (s, 1H, -C**H**=N in quinoxaline). M $^+$+1: 293.

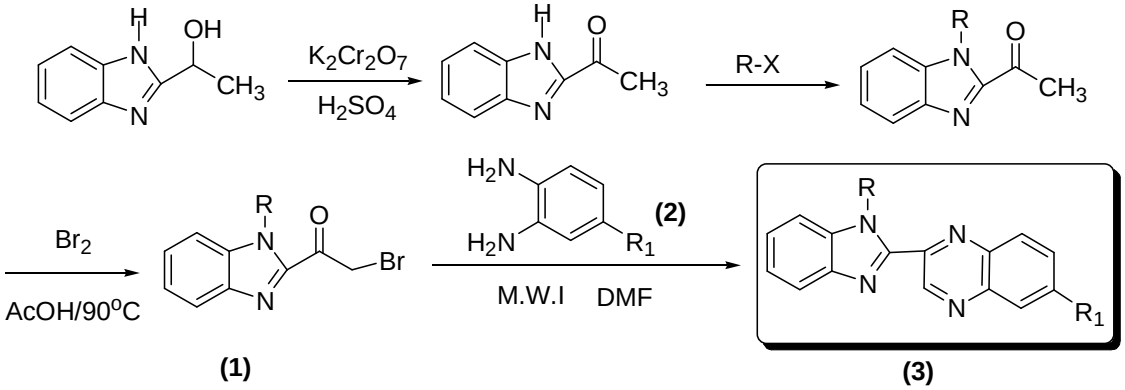
**6-Bromo-2-(1-benzyl-1H-benzimidazole-2yl)quinoxaline (3h)**: R=$CH_2$-$C_6H_5$, $R^1$=Br; Yield= 72% (Method A), 69% (Method B); Mp 118-20$^o$C; Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 6.3 (s, 2H, -C**H**$_2$), 7.2-8.1 (m, 13H, **aryl protons**), 9.8 (s, 1H, -C**H**=N in quinoxaline). ; M $^+$+1: 415

**6-Fluro-2-(1-benzyl-1H-benzimidazole-2yl)quinoxaline (3i)**: R=$CH_2$-$C_6H_5$, $R^1$=F; Its $^1$H-NMR (DMSO-$d_6$/TMS) showed signals at δ 6.3 (s, 2H, -C**H**$_2$), 7.2-8.1 (m, 13H, **aryl protons**), 9.8 (s, 1H, -C**H**=N in quinoxaline); M $^+$+1: 355.

## RESULTS AND DISCUSSION

Condensation of N-methyl-2-α-bromoacetylbenzimidazole **(1a)** with *o*-phenylenediamine **(2a)** using minimum quantity of DMF as a solvent under microwave irradiation afforded the corresponding 2-(1-methyl-1H-benzimidazole-2-yl)-quinoxaline **(3)** in excellent yields (scheme). The product was obtained by neutralizing residual mixture with sodium bicarbonate of its salt formed initially, which is identical with the product obtained in solution phase with respect to m.p., m.m.p, tlc, IR, $^1$H NMR and mass. Further, we observed that the yields obtained under microwave assisted synthesis are high compared to conventional method [19].

This reaction of **1a** with **2a** has been found to be a general one and has been extended to other N-alkyl substituted benzimidazole and substituted *o*-phenylenediamine and the products obtained were assigned the structures **3**, on the basis of their spectral and analytical data. The IR, $^1$H NMR and Mass spectra of the products are in consonance with benzimidazole structures and their m.p. are in agreement with those available in the literature [19]. The yields, m.p. and literature m.p. are given in Table 1. The reaction under microwave condition goes to completion within 10 minutes at the 50% power level.




**Scheme**

**Table I: Products obtained under Micro-wave irradiation**

| Compound | R | $R_1$ | M.P. (°C) | Yield (%) | Time (in min) |
|---|---|---|---|---|---|
| 3a | $CH_3$ | H | 190-91 [191-92][19] | 92 | 5 |
| 3b | $-CH_2-CH_3$ | H | 170[170-72][19] | 90 | 5 |
| 3c | $-CH_2-Ph$ | H | 165[164-66][19] | 86 | 10 |
| 3d | $CH_3$ | Br | 71[70-72][19] | 92 | 5 |
| 3e | $CH_3$ | F | 151[150-52][19] | 84 | 5 |
| 3f | $-CH_2-CH_3$ | Br | 77[78-80][19] | 89 | 5 |
| 3g | $-CH_2-CH_3$ | F | 49[48-50][19] | 88 | 5 |
| 3h | $-CH_2-Ph$ | Br | 119[118-20][19] | 80 | 10 |
| 3i | $-CH_2-Ph$ | F | 99[98-100][19] | 84 | 10 |

## CONCLUSION

In conclusion, all the 2-(1-alkyl/aralkyl-1H-benzimidazole-2-yl)-quinoxaline derivatives were obtained in good yields by the reaction of *o*-phenylenediamine with various N-alkyl/aralkyl 2-α-bromoacetylbenzimidazole in the presence of microwave irradiation.

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