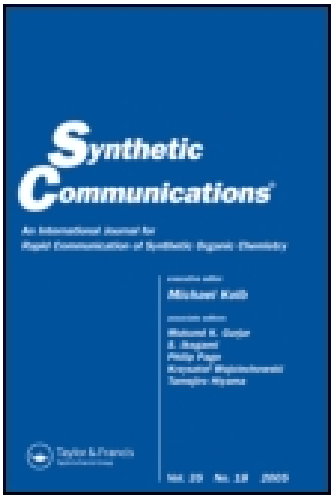

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# MK-10 Clay-Catalyzed Synthesis of 2-(2′,5′-Disubstituted-1′H-indol-3′-yl)-1H-benzo[d]imidazoles under Conventional and Microwave Irradiation

J. S. Biradar [a] & B. Sharanbasappa [a]
[a] Department of Studies in Chemistry , Gulbarga University , Gulbarga , Karnataka , India
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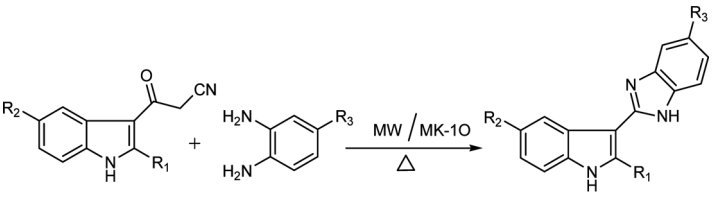
# MK-10 CLAY–CATALYZED SYNTHESIS OF 2-(2′,5′-DISUBSTITUTED-1′H-INDOL-3′-YL)-1H-BENZO[d]IMIDAZOLES UNDER CONVENTIONAL AND MICROWAVE IRRADIATION

**J. S. Biradar and B. Sharanbasappa**
*Department of Studies in Chemistry, Gulbarga University, Gulbarga, Karnataka, India*

## GRAPHICAL ABSTRACT




$R_1$ = Ph, Me, H; $R_2$ = Cl, Me, OMe, H; $R_3$ = Me, H

**Abstract** *The synthesis of benzimidazoles has been achieved in a one-pot reaction in excellent yield using a newly developed methodology. 2,5-Disubstituted-3-cyanoacetyl indoles were directly condensed with substituted orthophenylenediamine via microwave irradiation under neat, solid support, and conventional conditions in a short time to afford the corresponding products in good yields. Structures of the products thus obtained were confirmed by their melting points, infrared, $^1H$ NMR, $^{13}C$ NMR, and mass spectral data.*

**Keywords** Benzimidazoles; conventional method; environmentally benign; indole; microwave irradiation; solid support

## INTRODUCTION

In continuation of our ongoing interest in the green synthesis of indoles,[1–5] we have developed a mild and expedient novel synthesis for benzimidazole[6–10] incorporated with the indole nucleus using montmorillonite K10 clay as the catalyst. The method is highly efficient and free from drawbacks. A brief account of our work and its main findings as well as the advantages of this method over the existing synthetic routes is discussed in this communication. Montmorillonite K10 clay[11] is known to behave as both a protic and a Brønsted acid (Hammett acidity function,

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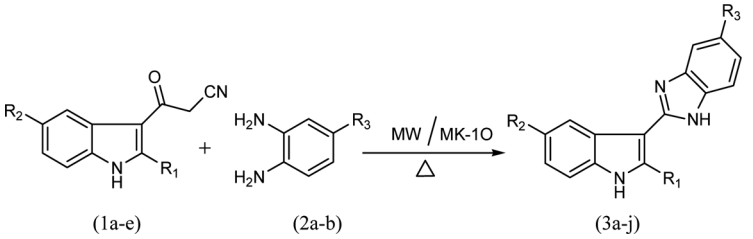
Address correspondence to J. S. Biradar, Professor of Organic Chemistry, Department of Studies in Chemistry, Gulbarga University, Gulbarga 585106, Karnataka State, India. E-mail: jsbiradar1@rediffmail.com




**Scheme 1.** $R_1 = Ph$, Me, H; $R_2 = Cl$, Me, OMe, H; $R_3 = Me$, H.

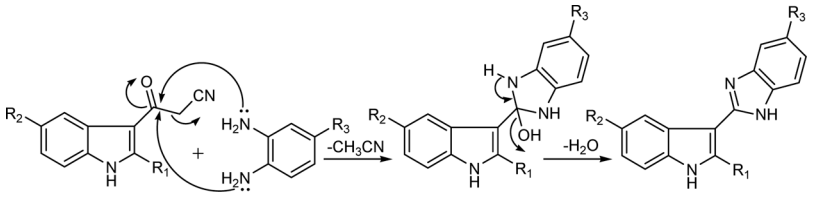
$H_0$: −5.5 to 5.9) and has a large specific surface area (500–760 $m^2/g$). We therefore used this clay in dimethylformamide (DMF; as an energy-transfer agent and homogenizer to increase the reaction temperature) reaction of 2,5-disubstituted-3-cyanoacetyl indole and substituted orthophenylenediamine under microwave irradiation [neat, solid supported (montmorillonite K-10 clay)] and conventional conditions (Scheme 1) that afforded 2-(2′,5′-disubstituted-1H-indol-3′-yl)-1H-benzo[d]imidazoles.

## RESULTS AND DISCUSSION

In the present investigation, the reaction (Scheme 1) was carried out with microwave irradiation by taking 2,5-disubstituted 3-cyanoacetyl indoles and substituted orthophenylenediamine in the presence of a MK-10 clay in DMF for 10 min. The products were obtained in good yields, and the use of MK-10 clay as the mineral support eliminates the necessity of an external base or strong acid for the synthesis of the title product, which was formed in reasonable purity. When the reaction was carried out using conventional heating, the products were obtained in moderate yields in 1–2 h (Table 1).

The reaction has also been performed under neat conditions (without solvent support or catalyst); however, no reaction occurred under neat conditions. It could be made successful by adding DMF. The role of DMF is that of an energy-transfer medium and homogenizer to increase the reaction temperature. However, products are formed in comparatively lesser yield in this case as compared to the solid-supported reaction.

Conventional synthesis suffers from disadvantages such as long reaction periods and poor yields (Table 2). Hence, we have developed a new, economical, safe,




**Scheme 2.** Possible reaction mechanism.

**Table 1.** Comparative study of the synthesis of **3a–e**

| Entry | Method | Conventional (reflux) Microwave power (%) | Reaction time (min) | Isolated yield (%) | |
|---|---|---|---|---|---|
| | | | | MW | Δ |
| **3a** | Δ (DMF) | Reflux | 60 | — | 58 |
| | MW (Neat) | 50 | 10 | Nil | — |
| | MW (DMF) | 50 | 10 | 80 | — |
| | MW (DMF + MK-10) | 50 | 10 | 92 | — |
| **3b** | Δ (DMF) | Reflux | 90 | — | 53 |
| | MW (Neat) | 50 | 10 | Nil | — |
| | MW (DMF) | 50 | 10 | 77 | — |
| | MW (DMF + MK-10) | 50 | 10 | 85 | — |
| **3c** | Δ (DMF) | Reflux | 60 | — | 56 |
| | MW (Neat) | 50 | 10 | Nil | — |
| | MW (DMF) | 50 | 10 | 80 | — |
| | MW (DMF + MK-10) | 50 | 10 | 90 | — |
| **3d** | Δ (DMF) | Reflux | 120 | — | 52 |
| | MW (Neat) | 50 | 10 | Nil | — |
| | MW (DMF) | 50 | 10 | 74 | — |
| | MW (DMF + MK-10) | 50 | 10 | 78 | — |
| **3e** | Δ (DMF) | Reflux | 60 | — | 53 |
| | MW (Neat) | 50 | 10 | Nil | — |
| | MW (DMF) | 50 | 10 | 70 | — |
| | MW (DMF + MK-10) | 50 | 10 | 80 | — |

environmentally benign, one-pot synthesis of novel 2-(2′,5′-disubstituted-1′H-indol-3′-yl)-1H-benzo[d]imidazoles under microwave irradiation. The method of synthesis (10 min) has given excellent yields (75–92%).

The infrared (IR) spectrum of compound **3a** has shown characteristic peaks at 3278 (N−H), 3188 (N−H), 2925 (C−H), 1635 (C=N), 1578 (C=C), and 748 (C-Cl) $cm^{-1}$. The $^1H$ NMR spectrum of **3a** displayed a downfield signal at δ 11.6 (s, 1H), integrating for one proton of indole, and at δ 10.4 (s, 1H), integrating for one proton of the benzimidazole NH. A multiplet was observed at δ 7.1–7.8 (m, 12H, ArH),

**Table 2.** Comparative data of conventional (A) and MW (B) methods for the synthesis of compounds **3a–j**

| Entry | $R_1$ | $R_2$ | $R_3$ | Conventional method | | Microwave method | | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Time (min) | Yield (%) | Time (min) | Power (%) | | |
| **3a** | Ph | Cl | H | 60 | 58 | 10 | 50 | 92 | 202–204 |
| **3b** | Ph | Me | H | 90 | 53 | 10 | 50 | 85 | 187–189 |
| **3c** | Ph | OMe | H | 60 | 56 | 10 | 50 | 90 | 193–195 |
| **3d** | Me | H | H | 120 | 52 | 10 | 50 | 78 | 277–279 |
| **3e** | H | H | H | 60 | 53 | 10 | 50 | 80 | 226–228 |
| **3f** | Ph | Cl | Me | 60 | 56 | 10 | 50 | 85 | 208–210 |
| **3g** | Ph | Me | Me | 90 | 55 | 10 | 50 | 83 | 178–180 |
| **3h** | Ph | OMe | Me | 90 | 60 | 10 | 50 | 88 | 167–169 |
| **3i** | Me | H | Me | 120 | 54 | 10 | 50 | 75 | 200–201 |
| **3j** | H | H | Me | 60 | 51 | 10 | 50 | 80 | 214–216 |

integrating for 12 aromatic protons. The $^{13}C$ NMR spectrum of **3a** displayed a downfield signal at δ 153, integrated for benzimidazole carbon, and at δ 145, 137, 132, 129, 128, 127, 122, 120, 119, 118, 116, 114, 112, and 100, integrated for aromatic carbons. The mass spectrum of compound **3a** has displayed molecular ion peaks at 343 (M+.) (76%), 345 (M + 2) (25%) and peaks at $m/z$ 252 (100%), 254 (33%), 226 (40%), 228 (13%), 217 (15%), 125 (18%), 127 (6%), and 118 (55%). This fragmentation pattern supported the formation of the title compound.

## EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer Fourier transform (FTIR)–spectrophotometer ($cm^{-1}$), and $^1H$ NMR spectra were recorded on a Bruker Avene II 400-MHz NMR spectrometer (chemical shifts in δ ppm downfield from tetramethylsilane as an internal reference). The mass spectra were recorded on a LC-MSD-Trap-SL instrument, and microwave reactions were carried out in an Onida 20STP21 800W (MO 20SG05101262) multimode domestic microwave oven.

### Conventional Method (3a–j)

A mixture of 2,5-disubstituted 3-cyanoacetyl indole (1 mmol) and substituted orthophenylenediamine (1 mmol) was refluxed with 5 ml of DMF in a given time (Table 2). The reaction mixture was allowed to cool to room temperature and poured into crushed ice. The solid thus obtained was dried and recrystallized from DMF and ethanol to afford the title compounds **3a–j** with 51–60% yield (Table 2).

### Microwave-Assisted Synthesis

**Neat reaction.** A mixture of 2,5-disubstituted 3-cyanoacetyl indole (1 mmol) and substituted orthophenylenediamine (1 mmol) were introduced in an open borosil glass vessel. This was subjected to microwave irradiation for 10 min with 50% microwave power (Table 1), and no products were found.

**Neat with DMF.** A mixture of 2,5-disubstituted 3-cyanoacetyl indole (1 mmol), substituted orthophenylenediamine (1 mmol), and DMF (1 ml) was introduced in an open borosil glass vessel. This was subjected to microwave irradiation for 10 min with 50% microwave power (Table 1) and gave an oily product, which solidified on standing. Washing this with ice cold water gave the crude product, which was recrystallized from DMF or ethyl alcohol to afford the title compounds with good yield (Table 2).

**Neat with DMF + solid support.** A mixture of 2,5-disubstituted 3-cyanoacetyl indole (1 mmol), substituted orthophenylenediamine (1 mmol), and DMF (1 ml) on 2 g of MK-10 clay was introduced in an open borosil glass vessel. This was subjected to microwave irradiation for 10 min with 50% microwave power (Table 1). The product was washed with ice-cold water and recrystallized from DMF or ethyl alcohol to give the title compound, which was in good purity (thin-layer chromatography) and yield (Table 2).

### Selected Data

**2-(5-Chloro-2-phenyl-1H-indol-3-yl)-1H-benzo[d]imidazole (3a).** Mp 202–204 °C; IR (KBr): $\nu_{max}/cm^{-1} = 3278$, 3188, 2925, 1635, 1578, 748. $^1H$ NMR (DMSO-$d_6$): $\delta = 11.6$ (br. s, 1H, NH), 10.4 (br. s, 1H, NH), 7.1–7.8 (m, 12H, ArH). $^{13}C$ NMR (DMSO-$d_6$): $\delta = 153$, 145, 137, 132, 129, 128, 127, 122, 120, 119, 118, 116, 114, 112, 100. MS: $m/z$ (%) = 343 (M+.) (76%), 345 (M + 2) (25%), 252 (100%), 254 (33%), 226 (40%), 228 (13%), 217 (15%), 125 (18%), 127 (6%), 118 (55%). Analysis calcd. for $C_{21}H_{14}ClN_3$: C, 73.36; H, 4.10; N, 12.22. Found: C, 73.38; H, 4.15; N, 12.25.

**2-(5-Methyl-2-phenyl-1H-indol-3-yl)-1H-benzo[d]imidazole (3b).** Mp 187–189 °C; IR (KBr): $\nu_{max}/cm^{-1} = 3295$, 3193, 2930, 1640, 1580. $^1H$ NMR (DMSO-$d_6$): $\delta = 11.5$ (br. s, 1H, NH), 10.3 (br. s, 1H, NH), 7.2–7.8 (m, 12H, ArH), 2.3 (s, 3H, $CH_3$). Analysis calcd. for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 12.99. Found: C, 81.75; H, 5.34; N, 12.95.

**2-(1H-Indol-3-yl)-1H-benzo[d]imidazole (3e).** Mp 226–228 °C; IR (KBr): $\nu_{max}/cm^{-1} = 3276$, 3201, 2927, 1617, 1582. $^1H$ NMR (DMSO-$d^6$): $\delta = 10.8$ (br. s, 1H, NH), 10.1 (br. s, 1H, NH), 7.0–7.9 (m, 9H, ArH). Analysis calcd. for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.25; H, 4.79; N, 18.07.

**2-(5-Chloro-2-phenyl-1H-indol-3-yl)-6-methyl-1H-benzo[d]imidazole (3f).** Mp 208–210 °C; IR (KBr): $\nu_{max}/cm^{-1} = 3283$, 3208, 2931, 1643, 1581, 745. $^1H$ NMR (DMSO-$d_6$): $\delta = 11.0$ (br. s, 1H, NH), 9.4 (br. s, 1H, NH), 7.0–7.8 (m, 11H, ArH), 2.2 (s, 3H, $CH_3$). Analysis calcd. for $C_{22}H_{16}ClN_3$: C, 73.84; H, 4.51; N, 11.74. Found: C, 73.88; H, 4.55; N, 11.79.

**6-Methyl-2-(5-methyl-2-phenyl-1H-indol-3-yl)-1H-benzo[d]imidazole (3g).** Mp 178–180 °C; IR (KBr): $\nu_{max}/cm^{-1} = 3286$, 3210, 2930, 1636, 1583. $^1H$ NMR (DMSO-$d_6$): $\delta = 10.8$ (br. s, 1H, NH), 10.0 (br. s, 1H, NH), 7.0–7.7 (m, 11H, ArH), 2.1 (s, 3H, $CH_3$), 2.4 (s, 3H, $CH_3$). Analysis calcd. for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.90; H, 5.73; N, 12.49.

**2-(1H-Indol-3-yl)-6-methyl-1H-benzo[d]imidazole (3j).** Mp 214–216 °C; IR (KBr): $\nu_{max}/cm^{-1} = 3281$, 3191, 2928, 1637, 1580. $^1H$ NMR (DMSO-$d_6$): $\delta = 10.7$ (br. s, 1H, NH), 9.3 (br. s, 1H, NH), 7.0–7.9 (m, 8H, ArH), 2.2 (s, 3H, $CH_3$). Analysis calcd. for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.75; H, 5.36; N, 17.02.



## ACKNOWLEDGMENTS

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