



# [BMIM]OH MEDIATED NEW SYNTHESIS 3-(1H-INDOL-3-YL)ACRYLONITRILE DERIVATIVES

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[Bmim]OH mediated new synthesis of 3-(1H-indol-3-yl)acrylonitrile derivatives **6** have been developed by the reaction of diethyl phthalate (**1**) with ethyl cyanoacetic acid hydrazide (**2**) to form 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile (**3**). Then compound **3** reacted with indole-3-aldehyde (**4**) by Knoevenagel condensation to form compound 2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles (**5**). Compounds **5** undergo alkylation with alkylating agents to form **6** with good yields. Compounds **6** could also be synthesized by alkylation of **4** followed by condensation with **3**.

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## INTRODUCTION

Ionic liquids as catalysts<sup>1</sup> and/or media<sup>2</sup> in reactions have been widely used in organic transformations due to their advantages such as good solvating ability, negligible vapor pressure, high polarity and ease of work-up. [Bmim]OH (1-butyl-3-methylimidazolium hydroxide) is one such task-specified ionic liquid which acts as reaction medium as well as a basic catalyst and has got various applications<sup>3</sup> in the field of synthetic methodology development.

Heterocycles containing the phthalazine moiety are of interest because they show some pharmacological and biological activities.<sup>4-5</sup> Mogilaiah et al<sup>6</sup> reported the synthesis of 1,8-naphthyridine-3-carbonylphthalazine-1,4-diones by the condensation of 1,8-naphthyridine-3-carboxylic acid hydrazides with phthalic anhydride using p-toluene sulphonic acid (PTSA) as a catalyst under solid state conditions. Mogilaiah et al<sup>7</sup> also reported the microwave irradiation of a mixture of 3-aryl-2-hydrazino-1,8-naphthyridines with phthalic anhydride in the presence of a catalytic amount of DMF resulting in 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthalazine-1,4-diones.

Indole derivatives continue to receive much attention in organic synthesis because of their biological activities.<sup>8,9</sup> Among them, 3-substituted indole is one of the 'privileged medicinal scaffold,' found in many biologically active compounds and natural products.<sup>10,11</sup> Through appropriate functional group modifications, these scaffolds are capable of providing ligands for a number of functionally and structurally discrete biological receptors. 3-Substituted indole scaffolds are found in a number of biologically active compounds especially with anticancer, anti-tumor,<sup>12</sup> hypoglycaemic, anti-inflammatory, analgesic and antipyretic activities.<sup>13-16</sup>

Keeping in view the potential importance of the phthalazine and indole ring containing compounds, we now wish to report our studies on reactions of phthalic anhydride with hydrazide derivatives and their further modifications.

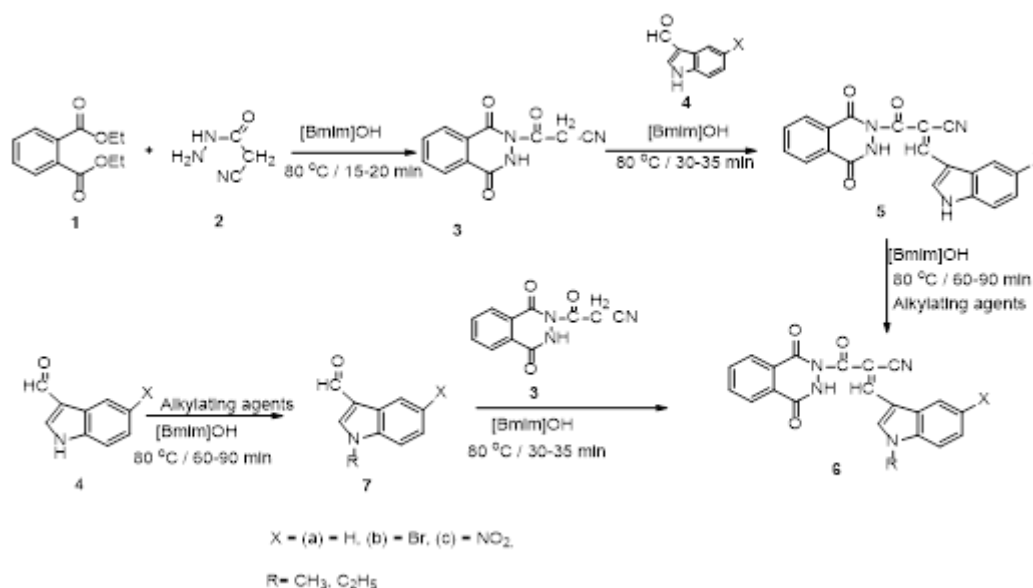
## RESULTS AND DISCUSSION

At first, we have developed the condensation of diethyl phthalate (**1**) (1 mmol), ethyl cyanoacetic acid hydrazide<sup>8</sup> (**2**) (1 mmol) to form 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile<sup>17</sup> (**3**) in the presence of 1-ethyl-3-methylimidazolium hydroxide solution [Bmim]OH (5 ml) at 80 °C for 15-20 min. Compound **3** (1 mmol) was reacted with indole-3-aldehyde (**4a**) (1 mmol) in the presence of [Bmim]OH (5 ml) at 80 °C for 30-35 min to form 2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles (**5a**) in 87 % yield on simple work-up of reaction mixture (TABLE 1, entry 1).

The gross structure of this product was assigned on the basis of its spectral data. Furthermore, the compound was supposed to be E-configuration on the presumption that bulky groups in a trans position would confer thermal stability on the molecule. This has been found to be the case by a careful examination of the Frame-work molecular models of both E and Z - configurations of **5a** wherein it was observed that there was a minimum number of steric interactions in the E - configuration.

The latter on alkylation of **5a** with an alkylating agent, i.e. dimethylsulfate (DMS) in the presence of [Bmim]OH (5 ml) at 80 °C for 60-90 min gave the corresponding indole-NH-alkylated derivatives **6a** with 85 % yield.

The above reaction was examined by carrying out the condensation of **3** with **4a** in the presence of different ionic liquids ([Bmim]Br, [Bmim]BF<sub>4</sub> and [Bmim]AlCl<sub>4</sub>) at different temperature (TABLE 1). However, the condensation of **3** with **4a** using [Bmim]OH as a catalyst and solvent media at 80 °C for 30 min gave the best yield (87 %) of **5a**. The alkylation reaction was also optimized by carrying out the alkylation of **5a** with DMS in the presence of different ionic liquids ([Bmim]Br, [Bmim]BF<sub>4</sub> and [Bmim]AlCl<sub>4</sub>) at different temperature (TABLE 1). However, the alkylation of **5a** with methyl bromide using [Bmim]OH as a catalyst and solvent media at 80 °C for 60 min gave the best yield (85 %) of **6a**.

Scheme 1. Synthesis of **6a-6f****Table 1.** Effect of ionic liquid and temperature on the reaction of **3** with **4a** yielding **5a**.

Ionic liquid	Temperature, °C	Time, min	Yield, %
[Bmim]OH	80	30	87
[Bmim]Br	80	45	72
[Bmim]BF <sub>4</sub>	80	50	63
[Bmim]AlCl <sub>4</sub>	80	60	54
[Bmim]OH	100	30	70
[Bmim]Br	100	35	62
[Bmim]BF <sub>4</sub>	100	40	61
Bmim]AlCl <sub>4</sub>	100	45	50
[Bmim]OH	RT	120	84
[Bmim]Br	RT	180	82
[Bmim]BF <sub>4</sub>	RT	190	75
[Bmim]AlCl <sub>4</sub>	RT	200	70

**Table 2.** Effect of ionic liquid & temperature on the reaction of **5a** with dimethyl sulfate yielding **6a**.

Ionic liquid	Temperature, °C	Time, min	Yield, %
[Bmim]OH	80	60	85
[Bmim]Br	80	75	80
[Bmim]BF <sub>4</sub>	80	70	82
[Bmim]AlCl <sub>4</sub>	80	90	80
[Bmim]OH	100	45	75
[Bmim]Br	100	55	73
[Bmim]BF <sub>4</sub>	100	65	70
Bmim]AlCl <sub>4</sub>	100	65	65
[Bmim]OH	RT	240	83
[Bmim]Br	RT	360	82
[Bmim]BF <sub>4</sub>	RT	360	81
[Bmim]AlCl <sub>4</sub>	RT	350	80

After having optimized the reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of **3** with **4a-4c** in the presence of [Bmim]OH at 80 °C for 30-35 min gave the corresponding compounds **5a-5c** in good yields. The latter on alkylation of **5a-5c** with alkylating agents in the presence of [Bmim]OH at 80 °C for 60-90 min gave the corresponding indole-NH-alkylated derivatives **6a-6f**. Using this strategy, alternatively, **6a-6f** were prepared by alkylation of **4a-4c** with alkylating agents in the presence of [Bmim]OH at 80 °C for 60-90 min to form **7a-7f** followed by Knoevenagel condensation of the initial product with **3** in the presence of [Bmim]OH at 80 °C for 30-40 min. All of the above reactions are summarized in Scheme 1.

## EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in open capillary tubes in a sulphuric acid bath. TLC was run on silica gel-G and visualization were done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. <sup>1</sup>H NMR spectra were recorded in DMSO-d<sub>6</sub> using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on an Agilent-LCMS instrument. Starting materials **1** and **4a-4c** were obtained from commercial sources and used as such.

### Preparation of **3**

A mixture of **1** (10 mmol), **2** (10 mmol) and [Bmim]OH (20 mL) was heated at 80 °C along with stirring and maintained until the completion of reaction as checked by TLC (15-20 min). To the resulting oily reaction mixture was added ethanol (30 mL) to force out the crude product from the polar ionic liquid reaction medium.

The separated solid mass was collected by filtration and dried in oven to obtain crude **3**. The later, were recrystallized from ethanol solvent to get the pure **3**.

**3**: M.p. 151–153 °C; IR (KBr) 17 : 3293-3518 cm<sup>-1</sup> (broad, medium, -NH-), 1748 cm<sup>-1</sup> (sharp, strong, -CO-), 1682 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1614 cm<sup>-1</sup> (sharp, strong, -CO- of amide group); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : δ 4.2 (s, 2H, CH<sub>2</sub>), 7.9-8.0 (m, 4H, Ar-H), 11.1 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 31.6, 36.9, 114.8, 124.8, 131.1, 136.2, 164.1, 164.8, 166.1; M<sup>+</sup>+1 = 230.

#### Preparation of **5** from **3** and **4**

A mixture of **3** (10 mmol), **4** (10 mmol) and [Bmim]OH (20 mL) was heated at 80 °C along with stirring and maintained until the completion of reaction as checked by TLC (35-40 min). To the resulting oily reaction mixture was added ethanol (30 ml) to force out the crude product from the polar ionic liquid reaction medium. The separated solid mass was collected by filtration and dried in oven to obtain crude **5**. The later, were recrystallized from ethanol solvent to get the pure **5**.

**5a**: M.p.: >220 °C; IR (KBr) 3017-3165 cm<sup>-1</sup> (broad, medium, -NH-), 1661 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1600 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 7.2-8.6 (m, 10H, Ar-H and C=CH), 11.1 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 12.6 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 92.8, 109.8, 112.9, 117.8, 118.4, 122.0, 123.6, 123.8, 127.1, 129.3, 132.1, 135.3, 136.1, 144.8, 162.0, 165.1; M<sup>+</sup>+1 = 357.

**5b**: M.p.: >220 °C; IR (KBr) 3012-3264 cm<sup>-1</sup> (broad, medium, -NH-), 1668 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1605 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 7.4-8.6 (m, 9H, Ar-H and C=CH), 11.2 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 12.4 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 92.6, 108.3, 111.4, 115.3, 117.3, 122.3, 123.4, 123.9, 127.3, 127.3, 130.3, 136.3, 138.3, 143.2, 161.4, 164.2; M<sup>+</sup>+1 = 435.

**5c**: M.p.: >220 °C; IR (KBr) 3016-3232 cm<sup>-1</sup> (broad, medium, -NH-), 1670 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1610 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 7.1-8.6 (m, 9H, Ar-H and C=CH), 11.3 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 12.4 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 91.3, 108.3, 111.5, 115.4, 118.3, 121.4, 123.5, 123.7, 124.2, 129.5, 132.3, 134.3, 135.2, 141.5, 160.1, 164.2; M<sup>+</sup>+1 = 402.

#### Preparation of **6** from **5** and alkylating agents

A mixture of **5** (10 mmol), alkylating agent (10 mmol) and [Bmim]OH (20 mL) was heated at 80 °C along with stirring and maintained until the completion of reaction as checked by TLC (60-90 min). To the resulting oily reaction mixture was added ethanol (30 ml) to force out the crude product from the polar ionic liquid reaction medium. The separated solid mass was collected by filtration and dried in oven to obtain crude **6**. The later, were recrystallized from ethanol solvent to get the pure **6**.

**6a**: M.p.: >230 °C; IR (KBr): 3316-3374 cm<sup>-1</sup> (broad, medium, -NH-), 1658 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1601 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 4.0 (s, 3H, CH<sub>3</sub>), 7.3-8.6 (m, 10H, Ar-H & C=CH), 11.1 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 33.8, 92.5, 108.8, 111.4, 117.6, 118.5, 122.4, 123.6, 123.8, 127.6, 129.3, 135.2, 135.3, 136.8, 144.0, 162.0, 165.1; M<sup>+</sup>+1 = 371.

**6b**: M.p.: >230 °C; IR (KBr): 3310-3390 cm<sup>-1</sup> (broad, medium, -NH-), 1650 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1610 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 4.1 (m, 2H, CH<sub>2</sub>), 2.2 (t, 3H, CH<sub>3</sub>), 7.3-8.4 (m, 10H, Ar-H and C=CH), 11.1 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 23.0, 34.6, 90.3, 104.4, 110.3, 114.6, 115.6, 120.3, 122.4, 124.4, 125.2, 128.2, 134.5, 135.5, 136.7, 143.5, 161.3, 164.4; M<sup>+</sup>+1 = 385.

**6c**: M.p.: >230 °C; IR (KBr) : 3315-3379 cm<sup>-1</sup> (broad, medium, -NH-), 1653 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1604 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 3.9 (s, 3H, CH<sub>3</sub>), 7.3-8.6 (m, 9H, Ar-H and C=CH), 11.0 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 33.2, 91.3, 107.3, 110.3, 114.3, 116.6, 121.3, 122.4, 123.7, 127.5, 129.4, 134.1, 135.2, 136.7, 144.1, 162.1, 165.3; M<sup>+</sup>+1 = 448.

**6d**: M.p.: >230 °C; IR (KBr) : 3312-3394 cm<sup>-1</sup> (broad, medium, -NH-), 1678 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1621 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 4.0 (m, 2H, CH<sub>2</sub>), 2.1 (t, 3H, CH<sub>3</sub>), 7.3-8.6 (m, 9H, Ar-H and C=CH), 11.3 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 23.2, 34.7, 91.2, 103.4, 109.2, 112.1, 114.5, 121.2, 122.3, 123.5, 125.3, 128.5, 133.1, 134.2, 135.2, 142.2, 161.9, 163.8; M<sup>+</sup>+1 = 462.

**6e**: M.p.: >230 °C; IR (KBr) : 3313-3379 cm<sup>-1</sup> (broad, medium, -NH-), 1659 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1600 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 4.1 (s, 3H, CH<sub>3</sub>), 7.2-8.9 (m, 9H, Ar-H and C=CH), 11.2 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 32.8, 91.5, 105.7, 110.3, 114.9, 118.4, 121.3, 122.4, 126.3, 127.5, 127.8, 134.1, 134.6, 135.9, 143.2, 162.0, 165.4; M<sup>+</sup>+1 = 416.

**6f**: M.p.: >230 °C; IR (KBr) : 3286-3379 cm<sup>-1</sup> (broad, medium, -NH-), 1659 cm<sup>-1</sup> (sharp, strong, -CO- of amide group), 1611 cm<sup>-1</sup> (sharp, strong, -CO-); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) : 4.3 (m, 2H, CH<sub>2</sub>), 2.3 (t, 3H, CH<sub>3</sub>), 7.3-8.5 (m, 9H, Ar-H and C=CH), 11.1 (s, 1H, -NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 23.3, 34.4, 91.4, 104.5, 111.4, 114.5, 114.9, 121.5, 121.4, 123.4, 124.2, 125.7, 133.1, 135.3, 135.8, 142.4, 161.2, 164.9; M<sup>+</sup>+1 = 430.

#### Preparation of **7a-7f** from **4a-4c** and alkylating agents

A mixture of **4** (10 mmol), alkylating agents (10 mmol) and [Bmim]OH (20 mL) was heated at 80 °C along with stirring and maintained until the completion of reaction as checked by TLC (60-90 min). To the resulting oily reaction mixture was added ethanol (30 mL) to force out the crude product from the polar ionic liquid reaction medium.

The separated solid mass was collected by filtration and dried in an oven to obtain crude **7**. The later was recrystallized from ethanol solvent to get the pure **7**.

### Preparation of 6a-6f from 7a-7f & 3

A mixture of **7** (10 mmol), **3** (10 mmol) and [Bmim]OH (20 mL) was heated at 80 °C along with stirring and maintained until the completion of reaction as checked by TLC (35-40 min). To the resulting oily reaction mixture was added ethanol (30 mL) to force out the crude product from the polar ionic liquid reaction medium. The separated solid mass was collected by filtration and dried in an oven to obtain crude **6**. The later was recrystallized from ethanol solvent to get the pure **6**.

### CONCLUSION

In summary, we have successfully developed syntheses of new 2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles (**6**) in two different routes under green conditions using ionic liquid without formation of any by-products with good yields.

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