

## A SIMPLE AND EFFICIENT SYNTHESIS OF NEW 6-ARYLIMINO-6H-INDOLO[2,1-*b*]QUINAZOLIN-12-ONES UNDER MICROWAVE IRRADIATION

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**Abstract-** A ring opening and selective reaction of isatoic anhydride with isatin-3-imine in the presence of catalytic amount of  $\text{KF-Al}_2\text{O}_3$ , a reusable catalyst, to yield a novel series of 6-arylimino-6H-indolo[2,1-*b*]quinazolin-12-one under microwave irradiation, is described.

Polyheterocyclic systems with quinazoline ring skeleton, for example, the pyrroloquinazolinoquinoline alkaloids, luotonin A (**1**)<sup>1</sup> and indolopyridoquinazolinone, rutaecarpin (**2**),<sup>2</sup> are isolated from plants. They are well known for their antitumor activity and intrinsic hypertensive, diuretic and uterotonic properties, respectively (Figure 1).

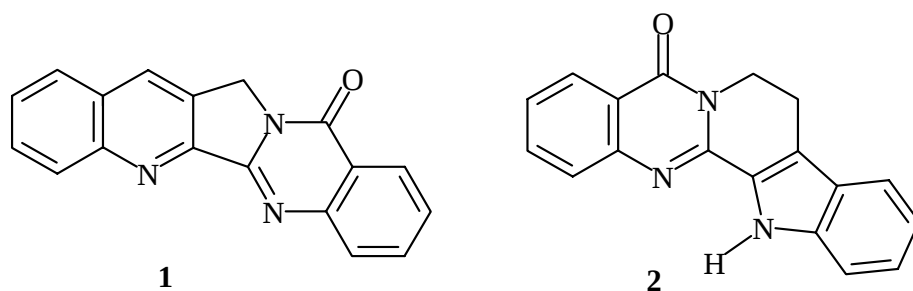


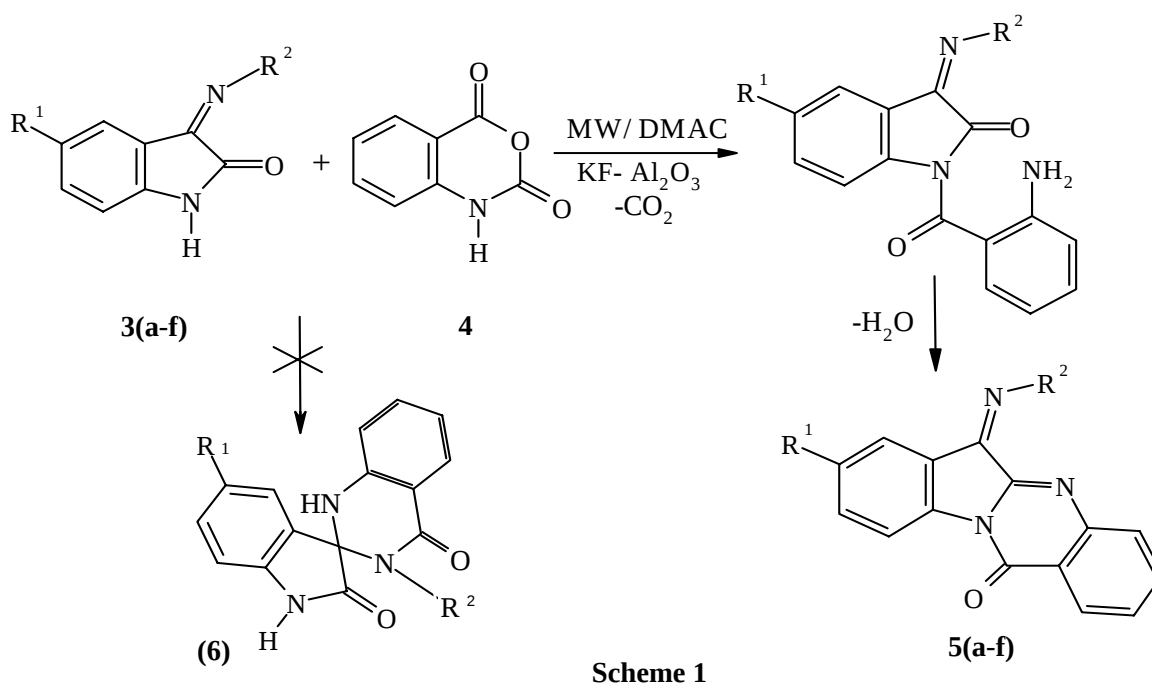
Figure 1

There exist numerous methods for the synthesis of quinazolinones and their derivatives.<sup>3</sup> Furthermore, the synthesis of these useful compounds has been reported by fusing the quinazolinone derivatives prepared from anthranilic acid,<sup>4</sup> by the cyclocondensation of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinolin with isatoic anhydride,<sup>5</sup> and by the condensation of 2-amino-*N*-(1-*H*-benzimidazol-2-yl)benzamide with orthoester,<sup>6</sup> under microwave irradiation.

Very recently, we have reported the preparation of quinazolinones derivatives by the three-component condensation reaction of isatoic anhydride, primary amine and urea or thiourea,<sup>7a</sup> and by oxidation of isatin-3-imines.<sup>7b</sup> Along this line, we planned the synthesis of new tetracyclic 6-arylimino-6H-indolo[2,1-*b*]quinazolin-

12-one (**5**), from isatoic anhydride<sup>8</sup> as a useful starting material and isatin-3-imine under microwave irradiation.<sup>9</sup>

We have found that the condensation of isatin-3-phenylimine (**3a**) with the isatoic anhydride (**4**) results in rapid formation of the 6-phenylimino-6*H*-indolo[2,1-*b*]quinazolin-12-one (**5a**) when the reaction was conducted in open vessels in a microwave oven (Scheme 1). In order to increase the energy input in a shorter time and provide a uniform heating, a small amount of *N,N*-dimethylacetamide (DMAC), an excellent energy – transfer solvent with a high dielectric constant, was added to the reaction mixture. In addition, we have also found that the reaction was promoted with KF-Al<sub>2</sub>O<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub>, but KF-Al<sub>2</sub>O<sub>3</sub> is highly efficient (Table 1).



Promoted by this success, we extended this reaction of isatoic anhydride with a range of other isatin-3-arylimines (**3b-f**) under similar conditions, furnishing the respective 6-arylimino-6*H*-indolo[2,1-*b*]quinazolin-12-one (**5 b-f**) in good to excellent yields.

**Table1.** Preparation of 6-arylimino-6*H*-indolo[2,1-*b*]quinazolin-12-ones (**5**) in the presence of KF-Al<sub>2</sub>O<sub>3</sub>

| 3  | 5  | R <sup>1</sup> | R <sup>2</sup>                     | Time <sup>a</sup><br>(min) | Yield <sup>a</sup><br>(%) <sup>c</sup> | Time <sup>b</sup><br>(min) | Yield <sup>b</sup><br>(%) <sup>c</sup> | mp<br>(°C)  |
|----|----|----------------|------------------------------------|----------------------------|----------------------------------------|----------------------------|----------------------------------------|-------------|
| 3a | 5a | H              | C <sub>6</sub> H <sub>5</sub>      | 4                          | 71                                     | 5                          | 42                                     | 234(decomp) |
| 3b | 5b | Br             | C <sub>6</sub> H <sub>5</sub>      | 4                          | 76                                     | 5                          | 24                                     | 255(decomp) |
| 3c | 5c | H              | 4-Cl-C <sub>6</sub> H <sub>4</sub> | 4                          | 79                                     | 5                          | 45                                     | 233(decomp) |
| 3d | 5d | Br             | 4-Cl-C <sub>6</sub> H <sub>4</sub> | 4                          | 83                                     | 5                          | 50                                     | 270(decomp) |
| 3e | 5e | H              | 4-Me-C <sub>6</sub> H <sub>4</sub> | 4                          | 73                                     | 5                          | 42                                     | 200(decomp) |
| 3f | 5f | Br             | 4-Me-C <sub>6</sub> H <sub>4</sub> | 4                          | 70                                     | 5                          | 42                                     | 238(decomp) |

a: Cat. KF-Al<sub>2</sub>O<sub>3</sub>. b: Cat. K<sub>2</sub>CO<sub>3</sub>. c: Yields of pure isolated product based on isatin-3-imine

In summary, we have describe a facile and efficient procedure for the preparation of new tetracyclic6-arylimino-

6*H*-indolo[2,1-*b*]quinazolin-12-ones using the inexpensive and non-toxic and easily available KF-Al<sub>2</sub>O<sub>3</sub> catalyst. The method offers several advantages including high yield of products, short reaction times, cleaner reaction, easy experimental work-up procedure. Surprisingly, this reaction is regioselective<sup>10</sup> in the preparation of 6-arylimino-6*H*-indolo[2,1-*b*]quinazolin-12-ones, since no detectable amount of compound (**6**) was observed and the imine group remained intact under the described reaction conditions, which makes it a useful process for the synthesis of 6-arylimino-6*H*-indolo[2,1-*b*]quinazolin-12-ones.

## EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were determined on a Bruker 500 DRX AVNCE instrument at 500 and 125 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. Microwave irradiation was carried out in a National oven, model 5250, at 2450 MHz.

**General procedures:** Isatin-3-arylimine (1 mmol) and isatoic anhydride (1 mmol, 163.13 mg) were mixed in *N,N*-dimethylacetamide (3 mL) in a tall beaker which was covered with a stemless funnel and subjected to microwave irradiation at 450 watts for 4 min (Table 1). After complete conversion, as indicated by TLC, the KF-Al<sub>2</sub>O<sub>3</sub> was separated and the reaction mixture was allowed to cool to rt. Then water was added to the mixture and the separated solid was filtered off and recrystallized from ethanol to give a pure product.

### Spectral data for product:

**6-Phenylimino-6*H*-indolo[2,1-*b*]quinazolin-12-one (5a):** orange crystalline solid, yield 71%, mp 234 °C (decomp), IR (KBr), ( $\nu_{\max}/\text{cm}^{-1}$ ): 1690 (C=O), 1648, 1581 (2C=N), <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 6.84 – 8.73 (13H, m, arom). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 118.23, 118.42, 119.59, 123.20, 125.77, 126.73, 127.65, 129.26, 130.03, 130.17, 130.48, 134.80, 135.32, 143.87, 147.47, 148.85 (arom), 150.91, 154.98 (2 C=N), 159.34 (C=O), MS (*m/z*, %): 323 (M<sup>+</sup>, 75), 322 (90), 295 (10), 246 (15), 205 (10), 77 (70), 51 (49). Anal. Calcd for C<sub>21</sub>H<sub>13</sub>N<sub>3</sub>O: C, 78.04; H, 4.02; N, 12.99. Found: C, 77.96; H, 3.96; N, 12.91.

**8-Bromo-6-phenylimino-6*H*-indolo[2,1-*b*]quinazolin-12-one (5b):** yellow brown crystalline solid, yield 76%, mp 255 °C (decomp), IR(KBr), ( $\nu_{\max}/\text{cm}^{-1}$ ): 1680 (C=O), 1653, 1580 (2 C=N), <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 6.93-8.62 (12 H, m, arom). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 118.13, 119.61, 119.87, 121.04, 123.03, 125.34, 127.62, 129.50, 130.02, 130.15, 130.26, 135.51, 137.32, 142.56, 147.38, 148.29 (arom), 150.35, 154.98 (2 C=N), 159.13 (C=O), MS (*m/z*, %): 402 (M<sup>+</sup>, 90), 404 (75), 406 (25), 374 (10), 325 (20), 77 (80), 51 (70). Anal. Calcd for C<sub>21</sub>H<sub>12</sub>N<sub>3</sub>OBr: C, 62.72; H, 2.98; N, 10.44. Found: C, 62.64; H, 2.90; N, 10.32.

**6-(4-Chlorophenylimino)-6*H*-indolo[2,1-*b*]quinazolin-12-one (5c):** dark orange crystalline solid, yield 79%, mp 233 °C (decomp), IR (KBr), ( $\nu_{\max}/\text{cm}^{-1}$ ): 1680 (C=O), 1641, 1573 (2 C=N), <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 6.95-

8.74 (12H, m, arom).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 118.31, 119.35, 119.92, 123.16, 126.59, 126.76, 127.66, 129.38, 130.14, 130.22, 131.16, 135.11, 135.36, 143.93, 147.32, 148.65, (arom), 149.18, 155.93 (2 C=N), 159.15 (C=O), MS ( $m/z$ , %): 358 ( $\text{M}^+$ , 50), 356 (90), 328 (10), 322 (25), 232 (10), 114 (15), 75 (90), 50 (50). Anal. Calcd for  $\text{C}_{21}\text{H}_{12}\text{N}_3\text{OCl}$ : C, 70.52; H, 3.35; N, 11.74. Found: C, 70.46; H, 3.26; N, 11.65.

**8-Bromo-6-(4-chlorophenylimino)-6H-indolo[2,1-b]quinazolin-12-one (5d)**: orange crystalline solid, yield 83%, mp 270 °C (decomp), IR (KBr), ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1685 (C=O), 1660, 1576 (2 C=N),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.05-8.64 (11 H, m, arom).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 119.75, 119.92, 120.84, 121.88, 123.01, 127.73, 129.23, 129.64, 130.28, 130.33, 131.83, 135.58, 137.69, 142.69, 147.28, 148.13 (arom), 148.44, 153.80 (2 C=N), 159.02 (C=O), MS ( $m/z$ , %): 436 ( $\text{M}^+$ , 50), 438 (30), 440 (10), 408 (10), 359 (15), 318 (10), 75 (50), 50 (30). Anal. Calcd for  $\text{C}_{21}\text{H}_{11}\text{N}_3\text{OBrCl}$ : C, 57.77; H, 2.52; N, 16.65. Found: C, 57.70; H, 2.44; N, 16.56.

**6-(4-Methylphenylimino)-6H-indolo[2,1-b]quinazolin-12-one(5e)**: orange-brown crystalline solid, yield 73%, mp 200 °C (decomp), IR (KBr), ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1685 (C=O), 1643, 1570 (2 C=N),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.64 (3H, s,  $\text{CH}_3$ ), 6.99-8.73 (12 H, m, arom).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 21.56 ( $\text{CH}_3$ ), 118.19, 118.44, 119.69, 123.15, 126.59, 126.66, 127.62, 129.16, 130.13, 130.36, 130.55, 134.63, 135.62, 143.78, 147.51, 148.26 (arom), 148.94, 154.73 (2 C=N), 159.36 (C=O), MS ( $m/z$ , %): 336 ( $\text{M}^+$ , 60), 309 (10), 260 (15), 91 (60), 65 (100), 44 (90). Anal. Calcd for  $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}$ : C, 78.35; H, 4.45; N, 12.45. Found: C, 78.26; H, 4.36; N, 12.37.

**8-Bromo-6-(4-methylphenylimino)-6H-indolo[2,1-b]quinazolin-12-one (5f)**: Brown crystalline solid, yield 70%, mp 238 °C (decomp), IR (KBr), ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1686 (C=O), 1639, 1600 (2 C=N),  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta_{\text{H}}$ : 1.38 (3H, s,  $\text{CH}_3$ ), 6.55-7.53 (11 H, m, arom).  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ )  $\delta_{\text{C}}$ : 21.46 ( $\text{CH}_3$ ), 118.25, 119.50, 119.86, 121.22, 123.03, 126.61, 127.64, 129.87, 130.02, 130.15, 130.26, 135.61, 137.34, 142.36, 147.38, 149.39 (arom), 150.25, 155.69 (2C=N), 158.13 (C=O), MS ( $m/z$ , %): 416 ( $\text{M}^+$ , 50), 388 (10), 325 (20), 91 (90), 65 (80). Anal. Calcd for  $\text{C}_{22}\text{H}_{14}\text{N}_3\text{OBr}$ : C, 63.50; H, 3.36; N, 10.09. Found: C, 63.42; H, 3.26; N, 9.98.

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