

## SYNTHESIS OF 1-ARYL-6,6-DIMETHYL-2-PHENYL-6,7-DIHYDRO-1H-INDOL-4(5H)-ONES BY TWO STEPS, IN A THREE-COMPONENT REACTION

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### ABSTRACT

An efficient method for the synthesis of 1-aryl-6,6-dimethyl-2-phenyl-6,7-dihydro-1H-indol-4(5H)-ones is achieved in two steps, using a three-component reaction of phenacyl bromide, dimedone and aniline derivatives in water-ethanol (1:1) under reflux conditions.

**Keywords:** Phenacyl bromide, Dimedone, Anilines, 1H-Indol-4(5H)-ones, Three-component reaction.

### INTRODUCTION

In recent years, nitrogen-containing heterocyclic compounds have been the focus of both chemists and biochemists due to their wide range of biological and pharmaceutical properties.<sup>1,2</sup>

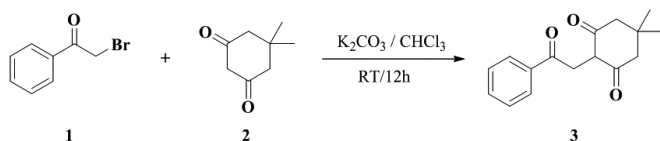
Among the various classes of nitrogen-containing heterocycles, indoles have many biological and pharmacological activities, such as GABA receptor ligands,<sup>3</sup> antipsychotic,<sup>4</sup> anticancer,<sup>5</sup> antioxidant,<sup>6</sup> antiproliferative agents,<sup>7</sup> anti-rheumatoid and anti-HIV,<sup>8,9</sup> and as soluble guanylatecyclase inhibitors.<sup>10,11</sup> Therefore, the synthesis and selective functionalization of indoles<sup>12-14</sup> and using indoles as starting materials for the synthesis of a series of alkaloids, pharmaceuticals and perfumes<sup>15</sup> have been the focus of researchers. A number of these are costly and harmful to the environment. By contrast, few synthetic methods based on green chemistry have been reported.<sup>16-18</sup>

None the less, the synthesis of indoles in aqueous or less toxic solvents by reducing the stages of the synthetic routes has been reported.<sup>19</sup> Multi-component reactions (MCRs) are powerful methods for the synthesis of organic compounds,<sup>20</sup> and are defined as convergent chemical processes where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials. They lead to the connection of three or more starting materials in a single synthetic operation with high atom economy and bond-forming efficiency, thereby increasing molecular diversity and complexity in a fast and often operational simplicity.<sup>21-22</sup>

A facile synthesis of substituted 6,7-dihydro-1H-indol-4(5H)-ones by reaction of cyclohex-2-enone and 2-oxo-2-(substituted phenyl)acetaldehyde has recently been reported.<sup>23</sup> In addition, Kaladevi and co-workers reported the reaction of 1-aryl-2-arylaminoethanones with substituted cyclohexane-1,3-diones in acetic acid through an intramolecular cyclization to form 1,3-dia-ryl-6,7-dihydro-1H-indol-4(5H)-ones.<sup>24</sup> In continuation of our interest in multi-component synthesis of nitrogen-containing heterocyclic compound,<sup>25</sup> herein we report the synthesis of 1-aryl-6,6-dimethyl-2-phenyl-6,7-dihydro-1H-indol-4(5H)-ones by two steps, involving a three-component reaction of phenacyl bromide, dimedone and various anilines in the presence of K<sub>2</sub>CO<sub>3</sub> in water-ethanol (1:1) under reflux conditions.

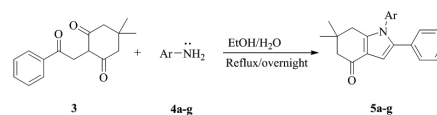
### RESULTS AND DISCUSSION

5,5-Dimethylcyclohexane-1,3-dione (**2**) was alkylated with phenacyl bromide (**1**), prepared from acetophenone via bromination with bromine in acetic acid at room temperature,<sup>26</sup> in the presence of K<sub>2</sub>CO<sub>3</sub>, to give the triketone<sup>27</sup> (**3**). (Scheme 1)



Scheme 1. Preparation of triketone (**3**)

The desired indoles were synthesized by adding anilines (**4a-g**) to triketone (**3**) in water-ethanol (1:1) and refluxing the reaction mixture overnight (Scheme 2). The products (**5a-g**) were obtained in good yields after recrystallization from methanol-acetone (1:1). The list of products (**5a-g**) along with their yields and melting points are given in Table 1.



**a;** Ar = C<sub>6</sub>H<sub>5</sub>      **b;** Ar = 2-MeC<sub>6</sub>H<sub>4</sub>      **c;** Ar = 3-MeC<sub>6</sub>H<sub>4</sub>      **d;** Ar = 4-MeC<sub>6</sub>H<sub>4</sub>  
**e;** Ar = 2,3-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>      **f;** Ar = 2-Me-3-ClC<sub>6</sub>H<sub>3</sub>      **g;** Ar = 1-C<sub>10</sub>H<sub>7</sub>

Scheme 2. Synthesis of 1H-indol-4(5H)-one derivatives

The improved procedure reported in this article is a simple and environmentally benign in comparison with other method mentioned in the literature.

The spectral data for all products is consistent with the assigned structures. In particular, in the <sup>1</sup>H-NMR spectra of the products, the indole 3-H is characterized by a singlet at δ = 6.79-6.93 ppm. The CH<sub>2</sub> next to the carbonyl group resonated as singlets at δ = 1.86-2.42 ppm while the CH<sub>2</sub> next to the pyrrole ring appear as singlets at δ = 2.12-2.53 ppm. Each of the two methyl groups on the aliphatic ring appear as singlets at δ = 0.85-1.27 ppm.

The <sup>13</sup>C-NMR spectra are characterized by the indole 3C resonances at δ 105.65 (**5a**), 110.34 (**5b**), 110.07 (**5c**), 104.87 (**5e**), 110.00 (**5f**), 105.21 (**5g**) (ppm). The CH<sub>2</sub> next to the carbonyl group resonates at δ 52.13 (**5a**), 46.13 (**5b**), 46.29 (**5c**), 52.20 (**5e**), 46.37 (**5f**), 52.21 (**5g**) (ppm). The C-7 CH<sub>2</sub> appeared at δ 37.08 (**5a**), 31.74 (**5b**), 31.74 (**5c**), 36.59 (**5e**), 31.71 (**5f**), 36.38 (**5g**) (ppm). The C=O absorption in the FT-IR spectra were observed at 1610-1660 cm<sup>-1</sup>.

### EXPERIMENTAL

Infrared spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR instrument using KBr discs. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in CDCl<sub>3</sub> relative to TMS as the internal standard. Elemental analyses were performed by using a Leco Analyzer 932. Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected.


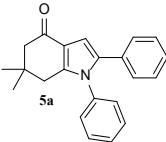

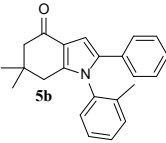

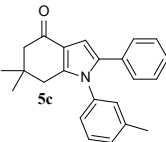

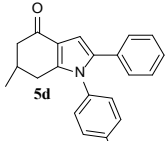

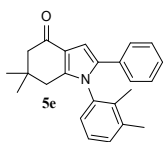

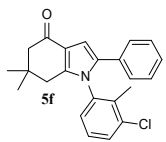

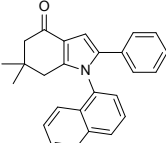



#### Preparation of triketone (**3**):

Phenacyl bromide<sup>26</sup> (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol) and anhydrous K<sub>2</sub>CO<sub>3</sub> (0.13 mmol) were stirred together in dry CHCl<sub>3</sub> (8 mL) for 12 h at 25 °C. The mixture was filtered and the residual potassium salt of the product was dissolved in water (60 mL), and the solution was acidified with HCl. The crude product (82%)<sup>28</sup> was collected, washed with water, and recrystallized from EtOH, m.p. 88 °C.

#### General Procedure for the synthesis of 1-aryl-6,6-dimethyl-2-phenyl-6,7-dihydro-1H-indol-4(5H)-ones (**5a-g**):

The aniline (2 mmol) was added to a solution of triketone (**3**) (1 mmol) in water-ethanol (1:1) (10 mL) and heated under reflux conditions overnight. The reaction mixture was cooled to room temperature and the product was then collected as a light pink precipitate which was washed with cold aqueous ethanol and purified by recrystallization from methanol-acetone (1:1) to give the desired products (**5a-g**) in 73-94% yield.

**Table 1.** The yields and melting points of products (**5a-g**).

Entry	Aniline	Indole	Yield (%)	M.p. (°C)
1	 4a	 5a	85	207
2	 4b	 5b	90	175
3	 4c	 5c	93	184
4	 4d	 5d	94	185
5	 4e	 5e	89	147
6	 4f	 5f	77	164
7	 4g	 5g	73	189
8	 4h	N.R	-	-
9	 4i	N.R	-	-
10	 4j	N.R	-	-

**6,6-Dimethyl-1,2-diphenyl-6,7-dihydro-1H-indol-4(5H)-one (5a):**

White solid, yield 85%, m.p. 207 °C [Lit.<sup>29</sup> 205 °C]. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 1.06 (s, 3H, Me), 1.10 (s, 3H, Me), 2.42 (s, 2H, CH<sub>2</sub>), 2.53 (s, 2H, CH<sub>2</sub>), 6.79 (s, 1H, Ar), 7.04-7.10 (m, 2H, Ar), 7.11-7.21 (m, 5H, Ar), 7.37-7.44 (m, 3H, Ar). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm): 28.64, 35.56, 37.08, 52.13, 105.65, 119.94, 126.87, 127.77, 128.14, 128.18, 128.26, 128.61, 129.34, 131.93, 136.33, 137.70, 144.71, 193.99. FT-IR ν<sub>max</sub> 3058, 2956, 2875, 1620, 1551, 1493, 1394, 1327, 1151, 1111, 771, 698 cm<sup>-1</sup>.

**6,6-Dimethyl-2-phenyl-1-(o-tolyl)-6,7-dihydro-1H-indol-4(5H)-one (5b):**

Light pink solid, yield 90%, m.p. 175 °C [Lit.<sup>30</sup> 174-176 °C]. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 0.89 (s, 3H, Me), 1.05 (s, 3H, Me), 1.86 (s, 2H, CH<sub>2</sub>), 2.17 (s, 2H, CH<sub>2</sub>), 2.23 (s, 3H, Me), 6.90-7.20 (m, 7H, Ar), 7.20-7.33 (m, 3H, Ar). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm): 17.61, 27.59, 28.72, 31.74, 46.13, 108.32, 110.34, 112.27, 125.72, 127.01, 127.56, 128.11, 129.72, 130.09, 130.38, 131.76, 134.93, 136.55, 137.72, 139.56, 185.39. FT-IR ν<sub>max</sub> 3056, 2954, 2872, 1626, 1550, 1490, 1394, 1328, 1150, 1109, 768, 700 cm<sup>-1</sup>.

**6,6-Dimethyl-2-phenyl-1-(m-tolyl)-6,7-dihydro-1H-indol-4(5H)-one (5c):**

Light pink solid, yield 93%, m.p. 184 °C [Lit.<sup>30</sup> 184-185 °C]. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 0.89 (s, 3H, Me), 1.05 (s, 3H, Me), 2.12 (s, 2H, CH<sub>2</sub>), 2.26 (s, 5H, CH<sub>2</sub>+Me), 6.79 (d, J = 6.9 Hz, 1H, Ar), 6.80 (s, 1H, Ar), 6.92 (d, J = 7.2 Hz, 1H, Ar), 6.95-7.03 (m, 4H, Ar), 7.05-7.16 (m, 3H, Ar). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm): 21.08, 27.57, 28.69, 30.08, 31.74, 46.29, 110.07, 112.63, 125.75, 126.90, 127.56, 127.64, 129.37, 127.99, 130.01, 130.44, 132.02, 134.48, 138.14, 138.25, 186.44. FT-IR ν<sub>max</sub> 3056, 2953, 1610, 1548, 1487, 1398, 1340, 1242, 1031, 763, 696 cm<sup>-1</sup>.

**6,6-Dimethyl-2-phenyl-1-(p-tolyl)-6,7-dihydro-1H-indol-4(5H)-one (5d):**

White solid, yield 94%, m.p. 185 °C [Lit.<sup>30</sup> 184-187 °C]. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 1.11 (s, 3H, Me), 1.27 (s, 3H, Me), 2.41 (s, 3H, Me), 2.43 (s, 2H, CH<sub>2</sub>), 2.52 (s, 2H, CH<sub>2</sub>), 6.79 (s, 1H, Ar), 7.02-7.05 (m, 2H, Ar), 7.08-7.10 (m, 2H, Ar), 7.17-7.23 (m, 5H, Ar). FT-IR ν<sub>max</sub> 2922, 2854, 1659, 1515, 1462, 1260, 1215, 1026, 808, 761 cm<sup>-1</sup>.

**1-(2,3-Dimethylphenyl)-6,6-dimethyl-2-phenyl-6,7-dihydro-1H-indol-4(5H)-one (5e):**

White solid, yield 89%, m.p. 147 °C (dec.). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 1.09 (s, 3H, Me), 1.12 (s, 3H, Me), 1.76 (s, 3H, Me), 2.19 (d, J = 17.1 Hz, 1H), 2.28 (s, 3H, Me), 2.33 (d, J = 16.2 Hz, 1H), 2.46 (d, J = 16.2 Hz, 1H), 2.47 (d, J = 17.1 Hz, 1H), 6.84 (s, 1H, Ar), 7.27-7.07 (m, 8H, Ar). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm): 13.96, 20.33, 27.99, 29.22, 35.58, 36.59, 52.20, 104.87, 119.66, 126.21, 126.84, 127.46, 127.69, 128.15, 130.52, 132.12, 134.76, 136.65, 136.84, 138.63, 145.06, 193.93. FT-IR ν<sub>max</sub> 2924, 2856, 1658, 1468, 1283, 1219, 1084, 771, 701 cm<sup>-1</sup>. Anal. Calc. for C<sub>24</sub>H<sub>25</sub>NO: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.88; H, 7.41; N, 7.28%.

**1-(3-Chloro-2-methylphenyl)-6,6-dimethyl-2-phenyl-6,7-dihydro-1H-indol-4(5H)-one (5f):**

Light pink solid, yield 77%, m.p. 164 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 0.86 (s, 3H, Me), 1.05 (s, 3H, Me), 1.87 (s, 2H, CH<sub>2</sub>), 2.21 (s, 3H, Me), 2.30 (s, 2H, CH<sub>2</sub>), 6.97 (t, J = 8.1 Hz, 1H, Ar), 7.00-7.15 (m, 6H, Ar), 7.17 (d, J = 8.1 Hz, 1H, Ar), 7.25 (d, J = 8.7 Hz, 1H, Ar). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm): 15.34, 27.46, 28.76, 29.70, 31.71, 46.37, 110.00, 112.70, 125.91, 127.27, 127.68, 128.14, 128.86, 128.97, 129.77, 131.55, 134.85, 135.12, 135.43, 139.02, 186.23. FT-IR ν<sub>max</sub> 3064, 2956, 2873, 1618, 1467, 1398, 1297, 1151, 1110, 1016, 767, 700 cm<sup>-1</sup>. Anal. Calc. for C<sub>23</sub>H<sub>22</sub>ClNO: C, 75.92; H, 6.09; N, 3.85. Found: C, 76.12; H, 5.91; N, 3.73%.

**6,6-Dimethyl-1-(naphthalene-1-yl)-2-phenyl-6,7-dihydro-1H-indol-4(5H)-one (5g):**

White solid, yield 73%, m.p. 189 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 1.05 (s, 3H, Me), 1.06 (s, 3H, Me), 2.17 (d, J = 16.5 Hz, 1H, CH<sub>2</sub>), 2.37 (d, J = 16.5 Hz, 1H, CH<sub>2</sub>), 2.45 (s, 2H, CH<sub>2</sub>), 6.93 (s, 1H, Ar), 7.04 (br s, 5H, Ar), 7.38 (t, J = 6.6 Hz, 2H, Ar), 7.51 (t, J = 7.2 Hz, 2H, Ar), 7.56 (t, J = 6.9 Hz, 1H, Ar), 7.95 (d, J = 7.8 Hz, 2H, Ar). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm): 28.06, 28.89, 35.54, 36.38, 52.21, 105.21, 119.88, 122.63, 125.28, 126.55, 126.92, 127.54, 127.78, 128.07, 128.42, 128.75, 129.41, 130.94, 131.89, 134.09, 134.32, 137.59, 146.16, 194.07. FT-IR ν<sub>max</sub> 3056, 2955, 2871, 1660, 1600, 1554, 1464, 1412, 1218, 1148, 758, 695 cm<sup>-1</sup>. Anal. Calc. for C<sub>26</sub>H<sub>23</sub>NO:

C, 85.45; H, 6.34; N, 3.83. Found: C, 85.33; H, 6.45; N, 3.72%.

**CONCLUSIONS**

In conclusion, we have successfully developed a facile, efficient procedure for the synthesis of 1-aryl-6,6-dimethyl-2-phenyl-6,7-dihydro-1H-indol-4(5H)-ones by two steps, including a three-component reaction in water-ethanol under reflux. The advantageous features of this procedure are, high yields, operational simplicity, availability of starting materials and the use of water-ethanol as an environmentally friendly solvent.

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