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## SYNTHESIS OF 1,2-DISUBSTITUTED BENZIMIDAZOLES AND 2-SUBSTITUTED BENZOTHAZOLES CATALYZED BY HCl-TREATED *TRANS*-3,5-DIHYDROPEROXY-3,5-DIMETHYL-1,2-DIOXOLANE

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**Abstract** – The catalytic effect of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane in the presence of HCl has been explored in one-pot condensation reaction of *o*-phenylenediamines and *o*-aminobenzenethiol with a variety of aldehydes into their corresponding 2-aryl-1-arylmethylimidazoles and 2-arylbenzothiazoles respectively. The reactions were conducted under mild conditions in MeCN at room temperature to afford the products in excellent yields.

Benzimidazole and benzothiazole nuclei are of significant importance to medicinal industry.<sup>1,4</sup> Many benzimidazole and benzothiazole derivatives exhibit vital biological activities as neuropeptide YY1 receptor antagonism,<sup>5</sup> 5-lipoxygenase inhibitor for use as antiallergic agents,<sup>6</sup> factor Xa (FXa) inhibitors,<sup>7</sup> and poly (ADP-ribose) polymerase (PARP) inhibitors.<sup>8</sup> In addition, these classes of heterocyclic systems have found commercial applications in several therapeutic area as antiulcer, antihypertensive, antimicrobial,<sup>9</sup> antituberculosis,<sup>10</sup> antifungal,<sup>11</sup> antitumor,<sup>12</sup> and antihistamine agents,<sup>13</sup> as well as agents in treatment of interstitial cystitis.<sup>14</sup> Also, these compounds have found industrial uses as antioxidants,<sup>15</sup> vulcanization accelerators,<sup>16</sup> fluorescents,<sup>17</sup> photochromic agents,<sup>18</sup> and are considered as very important intermediates in organic reactions.<sup>19</sup> Therefore, medicinal and industrial chemists consider these benzimidazole- and benzothiazole-containing heterocycles to be promising compounds and pay considerable attention towards the development of efficient approaches to these compounds.

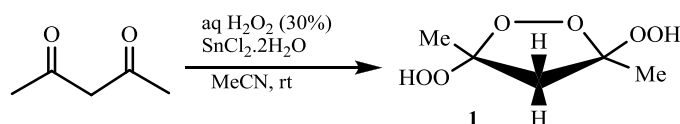
Almost all the existing methods for the synthesis of these heterocycles including the condensation of carboxylic acids,<sup>20</sup> acid chlorides,<sup>21</sup> nitriles,<sup>22</sup> orthoesters,<sup>23</sup> amids,<sup>24</sup> esters,<sup>25</sup> or aldehydes<sup>26</sup> with *o*-aminobenzenethiols and *o*-phenylenediamines (OPD) suffer from certain synthetic shortcomings such

as rigid conditions, poor yields, co-occurrence of several side reactions, use of toxic and costly catalysts and/or solvents.

Other synthetic routes employ microwave-assisted reaction of *o*-aminobenzenethiol with  $\beta$ -chloro cinnamaldehydes,<sup>27</sup> palladium-catalyzed direct coupling of benzothiazoles with arylhalides,<sup>28</sup> palladium-catalyzed condensation of arylhalides with *o*-aminobenzenethiol followed by dehydrative cyclization,<sup>16</sup> and reaction of copper(I) thiobenzoate with 2-iodoanilines.<sup>15</sup> In recent years, several simple one-step procedures have been developed for the synthesis of benzothiazoles and benzimidazoles using various catalytic systems.<sup>29</sup> However, these methods also suffer from the above-mentioned drawbacks. Indeed, the development of new and more benign synthetic methods is still in high demand. Bahrami *et al.*,<sup>30</sup> have utilized H<sub>2</sub>O<sub>2</sub> in HCl in oxidative cyclocondensation of phenylenediamines with aldehydes to synthesize benzimidazoles. Mamedov *et al.*,<sup>31</sup> have reported a novel synthesis of benzimidazoles from quinoxalinones and arylenediamines. Recently, use of silica gel-supported heteropoly acid,<sup>32</sup> and silica-supported ZnCl<sub>2</sub>,<sup>33</sup> in the synthesis of both benzothiazoles and benzimidazoles have been reported. Polymer-bound esters,<sup>34</sup> and PEG-mediated systems<sup>35</sup> have received considerable interest in the synthesis of benzothiazoles and benzimidazoles.

In continuation of our studies to explore new and cleaner approaches towards the heterocyclic compounds,<sup>36,37</sup> and also the synthesis and applications of *gem*-dihydroperoxides as versatile and high potent oxygen transfer agents in various organic transformations,<sup>38-40</sup> we report herein the novel use of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane in combination with HCl to effect the one-pot condensation of *o*-phenylenediamines and *o*-aminobenzenethiol with aldehydes into corresponding 2-aryl-1-arylmethylbenzimidazoles and 2-arylbenzothiazoles respectively. *Trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane has been prepared based on our previously reported method,<sup>51</sup> as a white crystalline solid in high yield (85%) from the SnCl<sub>2</sub>·2H<sub>2</sub>O-catalyzed reaction of acetylacetone with aqueous (30%) hydrogen peroxide (Scheme 1).

The reactions proceeded almost rapidly under mild conditions at room temperature in acetonitrile to convert the aldehydes **2** into 2-aryl-1-arylmethylbenzimidazoles **3** (Table 1) and 2-arylbenzothiazoles **4** (Table 2) respectively in high to excellent yields (Scheme 2).



**Scheme 1**



Scheme 2

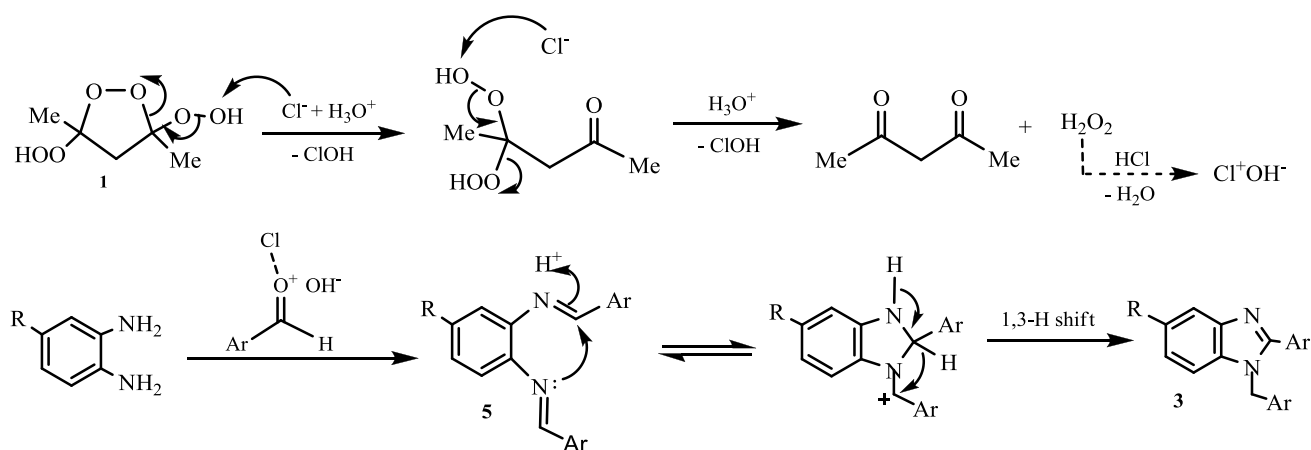
In order to establish the conditions for the titled reactions, we initially examined a model reaction choosing *o*-phenylenediamine (1 mmol)/or *o*-aminobenzenethiol (1 mmol) and 4-chlorobenzaldehyde (2.2 mmol) (entry 2) as test compounds. We also examined different solvents such as EtOH, Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, hexane, MeCN, 1,4-dioxane and DMF. It was found that, the best yields for the corresponding benzimidazole (96%) and benzothiazole (94%) are obtained when the reactions were conducted under stirring at room temperature in acetonitrile as the solvent of choice. Use of the aldehyde in slightly excess amount (10%) was found useful to prevent the formation of 2-arylbenzimidazole as the probable side product.<sup>39</sup> Stirring for further prolonged times or the use of excess amount of the reagent **1** (1.2 mmol) in the reaction resulted in comparable or in some cases reduced yields of the products.

To develop the scope of the reaction, various other aldehydes carrying different substituents were subjected to condensation with *o*-phenylenediamine or *o*-aminobenzenethiol under the optimized reaction conditions (stirring at room temperature in MeCN). The experimental results are summarized in Tables 1 and 2. Almost all the reactions proceeded smoothly with high selectivity in relatively short reaction times to afford the corresponding 2-aryl-1-arylmethyl-1H-benzimidazoles **3** and 2-aryl-1H-benzothiazoles **4** respectively in 98-88% and 96-85% yields.

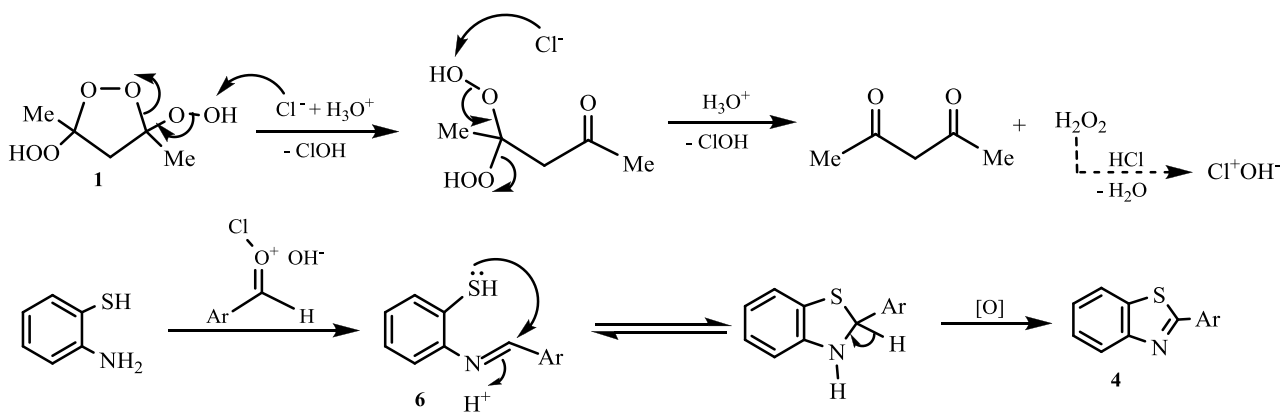
It is important to note that, *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane operates quite safely in these reactions with no explosion as long as the reactions are conducted at room temperature. Also, this compound tends to smoothly decompose on standing at normal temperatures. However, like many other peroxidic compounds, *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane is expected to be potentially explosive. Therefore, as mentioned in the experimental section, special precautions in handling of this compound are required, particularly heating to higher temperatures should be avoided.

A possible mechanism to explain the formation of the 1,2-disubstituted benzimidazoles **3** from *o*-phenylenediamine and aldehydes **2** under the promotion of the oxidant **1** in the presence of HCl is depicted in Scheme 3. According to our previous report,<sup>37</sup> and as suggested by Zelenin *et al.*,<sup>41</sup> the reaction probably occurs with the formation of diarylidene-*o*-phenylenediamine **5**, followed successively by cyclization and 1,3-hydride transfer. As shown in this Scheme, the first condensation step to yield the diarylidene-*o*-phenylenediamine **5** intermediate is probably catalyzed by the stronger Cl<sup>+</sup> ion which is

likely generated *in situ* by the effect of HCl on *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane **1**. This is confirmed by conducting the reaction with benzaldehyde at room temperature in the absence of the oxidant **1** which resulted in very low yield (24%) of the expected product **3a** after 6 h stirring at room temperature. However, a separately prepared diarylidene-*o*-phenylenediamine from the reaction of *o*-phenylenediamine with two equimolar amount of benzaldehyde in AcOH at 100 °C, was rapidly cyclized to **3a** (94%) under a catalytic amount of HCl. This can be indicative that the Cl<sup>+</sup> ion is most likely involved as a much stronger Lewis acid in the first condensation step to provide the intermediate **5**.



Similarly, the same *in situ* generation of Cl<sup>+</sup> ion is probably responsible for the activation of the aldehydes in the first condensation step with *o*-aminobenzenethiol to yield an intermediate arylidene-*o*-mercaptophenylamine **6**. Successive cyclization of the intermediate **6** in the presence of HCl followed by oxidation affords the expected products **3** (Scheme 4).<sup>45,46</sup>



**Table 1.** *Trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane-promoted synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles **3a-r** in HCl<sup>a</sup>

| Entry | Product <sup>b</sup> | Ar   | R  | Time (min) | Yield <sup>c</sup> (%) | Mp (°C) |                       |
|-------|----------------------|--|----|------------|------------------------|---------|-----------------------|
|       |                      |  |    |            |                        | Found   | Reported              |
| 1     | <b>3a</b>            | C <sub>6</sub> H <sub>5</sub>                    | H  | 20         | 96                     | 130-132 | 133-135 <sup>42</sup> |
| 2     | <b>3b</b>            | 4-ClC <sub>6</sub> H <sub>4</sub>                | H  | 30         | 94                     | 135-137 | 137 <sup>44</sup>     |
| 3     | <b>3c</b>            | 2-ClC <sub>6</sub> H <sub>4</sub>                | H  | 28         | 90                     | 154-156 | 155 <sup>44</sup>     |
| 4     | <b>3d</b>            | 4-MeC <sub>6</sub> H <sub>4</sub>                | H  | 25         | 95                     | 126-128 | 125-127 <sup>42</sup> |
| 5     | <b>3e</b>            | 4-NCC <sub>6</sub> H <sub>4</sub>                | H  | 24         | 90                     | 185-187 | 187-188 <sup>43</sup> |
| 6     | <b>3f</b>            | 4-MeOC <sub>6</sub> H <sub>4</sub>               | H  | 21         | 93                     | 132-134 | 129-131 <sup>42</sup> |
| 7     | <b>3g</b>            | 2-MeOC <sub>6</sub> H <sub>4</sub>               | H  | 24         | 94                     | 152-154 | 151 <sup>44</sup>     |
| 8     | <b>3h</b>            | 4-HOC <sub>6</sub> H <sub>4</sub>                | H  | 25         | 90                     | 256-258 | 254-256 <sup>43</sup> |
| 9     | <b>3i</b>            | 2-HOC <sub>6</sub> H <sub>4</sub>                | H  | 27         | 88                     | 210-212 | 207-208 <sup>43</sup> |
| 10    | <b>3j</b>            | 4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> | H  | 32         | 87                     | 154-156 | 152-155 <sup>42</sup> |
| 11    | <b>3k</b>            | 4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>  | H  | 32         | 91                     | 190-192 | 192 <sup>44</sup>     |
| 12    | <b>3l</b>            | 2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>  | H  | 30         | 90                     | 116-118 | 118 <sup>44</sup>     |
| 13    | <b>3m</b>            | 4-NCC <sub>6</sub> H <sub>4</sub>                | H  | 25         | 88                     | 188-190 | 187-188 <sup>43</sup> |
| 14    | <b>3n</b>            | 2-Furyl  | H  | 42         | 85                     | 96-98   | 96 <sup>44</sup>      |
| 15    | <b>3o</b>            | C <sub>6</sub> H <sub>5</sub>                    | Me | 28         | 93                     | 188-190 | New                   |
| 16    | <b>3p</b>            | 4-MeC <sub>6</sub> H <sub>4</sub>                | Me | 30         | 90                     | 160-162 | New                   |
| 17    | <b>3q</b>            | 4-MeOC <sub>6</sub> H <sub>4</sub>               | Me | 27         | 90                     | 182-184 | New                   |

<sup>a</sup> Conditions: aldehyde **2** (2.2 mmol), *o*-phenylenediamine (1 mmol), reagent **1** (1 mmol), MeCN (8 mL), HCl (3 mmol), room temperature.

<sup>b</sup> All the products are known.<sup>42-44</sup>

<sup>c</sup> Isolated yield.

**Table 2.** *Trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane-promoted synthesis of 2-aryl-1*H*-benzothiazoles **4a-p** in HCl<sup>a</sup>

| Entry | Product <sup>b</sup> | Ar  | Time (min) | Yield <sup>c</sup> (%) | Mp (°C) |                        |
|-------|----------------------|---|------------|------------------------|---------|------------------------|
|       |                      |   |            |                        | Found   | Reported <sup>36</sup> |
| 1     | <b>4a</b>            | C <sub>6</sub> H <sub>5</sub>                   | 15         | 94                     | 111-113 | 110-112                |
| 2     | <b>4b</b>            | 4-ClC <sub>6</sub> H <sub>4</sub>               | 17         | 90                     | 114-116 | 116-117                |
| 3     | <b>4c</b>            | 2-ClC <sub>6</sub> H <sub>4</sub>               | 22         | 88                     | 84-86   | 81-83                  |
| 4     | <b>4d</b>            | 4-MeC <sub>6</sub> H <sub>4</sub>               | 16         | 92                     | 87-89   | 85-87                  |
| 5     | <b>4e</b>            | 2-MeC <sub>6</sub> H <sub>4</sub>               | 17         | 90                     | 50-52   | 52-54                  |
| 6     | <b>4f</b>            | 4-MeOC <sub>6</sub> H <sub>4</sub>              | 18         | 92                     | 120-122 | 119-121                |
| 7     | <b>4g</b>            | 2-MeOC <sub>6</sub> H <sub>4</sub>              | 20         | 91                     | 100-102 | 99-102                 |
| 8     | <b>4h</b>            | 4-HOC <sub>6</sub> H <sub>4</sub>               | 22         | 89                     | 228-230 | 227-228                |
| 9     | <b>4i</b>            | 2-HOC <sub>6</sub> H <sub>4</sub>               | 21         | 88                     | 126-128 | 122-124                |
| 10    | <b>4j</b>            | 2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> | 14         | 89                     | 131-133 | 133-135                |
| 11    | <b>4k</b>            | 3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> | 16         | 91                     | 180-182 | 182-184                |
| 12    | <b>4l</b>            | 4-NCC <sub>6</sub> H <sub>4</sub>               | 13         | 88                     | 163-165 | 165-166                |
| 13    | <b>4m</b>            | 4-BrC <sub>6</sub> H <sub>4</sub>               | 13         | 92                     | 128-130 | 129-131                |
| 14    | <b>4n</b>            | 3-BrC <sub>6</sub> H <sub>4</sub>               | 17         | 90                     | 82-84   | 84-86                  |
| 15    | <b>4o</b>            | 4-FC <sub>6</sub> H <sub>4</sub>                | 13         | 90                     | 100-102 | 98-100                 |
| 16    | <b>4p</b>            | 2-Furyl   | 21         | 87                     | 101-103 | 100-103                |

<sup>a</sup> Conditions: aldehyde **2** (1 mmol), *o*-aminobenzenethiol (1 mmol), reagent **1** (1 mmol), MeCN (8 mL), HCl (3 mmol), room temperature.

<sup>b</sup> All the products are known.<sup>36</sup>

<sup>c</sup> Isolated yield.

In summary, *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane in combination with HCl has been explored as a highly selective and efficient oxygen releasing reagent to catalyze the condensation reactions of *o*-phenylenediamines and *o*-aminobenzenethiol with aromatic aldehydes. The reactions proceed under mild conditions at room temperature in acetonitrile to afford the corresponding 2-aryl-1-arylmethyl-1*H*-benzimidazoles and 2-aryl-1*H*-benzothiazoles respectively in high to excellent yields.

## EXPERIMENTAL

Chemicals used in this work were purchased from Fluka and Merck chemical companies and used without purification. IR spectra were recorded on a Perkin Elmer GX FT IR spectrometer from KBr pellets. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured for samples in CDCl<sub>3</sub> with a JEOL FX 90Q instrument at 90 and 22.5 MHz respectively, using Me<sub>4</sub>Si as internal standard. Melting points were measured on a SMPI apparatus.

*Caution:* Although we did not encounter any problem with *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane **1**, it is potentially explosive and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood and transition metal salts or heating should be avoided.

### General procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles **3a-q**:

To a mixture of *o*-phenylenediamine (1 mmol) and aldehyde **2** (2.2 mmol) in MeCN (8 mL), was added *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane **1** (1 mmol). Then 37% aqueous HCl (3 mmol) was added and the resulting mixture was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction as monitored by TLC (*n*-hexane/EtOAc; 2:1), 3M Na<sub>2</sub>SO<sub>3</sub> (1 mL) was added to quench the reaction and stirring was let to continue for a further 15 min. Then, the reaction mixture was diluted with distilled water (15 mL) and filtered to leave a solid which was crystallized from EtOH (96%) to obtain pure product **3** (Table 1). All the products were characterized by their physical and spectral (IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR) analysis and compared with the reported data.<sup>42-44</sup>

### 1-Benzyl-5-methyl-2-phenyl-1*H*-1,3-benzimidazole (**3o**)

Mp 188-190 °C; IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3051, 2926, 1594, 1549, 1502, 1448, 13.71, 1060, 711, 694. MS, *m/z* (%): 298 (M<sup>+</sup>). <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  2.44 (3H, s, CH<sub>3</sub>), 5.50 (2H, s, CH<sub>2</sub>), 7.00-7.68 (13H, m, Ar-H). <sup>13</sup>C NMR (22.5 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  20.2, 47.7, 110.0, 119.4, 122.6, 123.3, 125.0, 128.0, 129.8, 132.8, 134.5, 135.3, 142.5, 145.3, 149.5, 151.6, 154.3. *Anal.* Calcd for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>: C, 84.56; H, 6.04; N, 9.39%. Found: C, 84.52; H, 5.92; N, 9.34%.

### 5-Methyl-1-(4-methylbenzyl)-2-(4-methylphenyl)-1*H*-1,3-benzimidazole (**3p**)

Mp 160-162 °C; IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3026, 2905, 1597, 1573, 1497, 1396, 1332, 1134, 1048, 963, 823, 745, 690. MS,  $m/z$  (%): 326 ( $M^+$ ).  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.24 (3H, s,  $\text{CH}_3$ ), 2.45 (3H, s,  $\text{CH}_3$ ), 2.52 (3H, s,  $\text{CH}_3$ ), 5.50 (2H, s,  $\text{CH}_2$ ), 7.10-7.88 (11H, m, Ar-H).  $^{13}\text{C}$  NMR (22.5 MHz,  $\text{DMSO-d}_6$ ):  $\delta_{\text{C}}$  20.4, 21.2, 21.4, 48.3, 110.3, 119.5, 122.8, 123.2, 125.6, 126.8, 128.6, 129.2, 129.7, 133.5, 135.8, 137.1, 139.4, 143.6, 154.7. *Anal.* Calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2$ : C, 84.66; H, 6.74; N, 8.58%. Found: C, 84.63; H, 6.68; N, 8.52%.

### 1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-5-Methyl-1H-1,3-benzimidazole (3p)

Mp 182-184 °C; IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3083, 3056, 3025, 2924, 1597, 1497, 1353, 1293, 1117, 1093, 973, 830, 691. MS,  $m/z$  (%): 358 ( $M^+$ ).  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.50 (3H, s,  $\text{CH}_3$ ), 3.88 (3H, s,  $\text{OCH}_3$ ), 3.92 (3H, s,  $\text{OCH}_3$ ), 5.66 (2H, s,  $\text{CH}_2$ ), 7.00-7.98 (11H, m, Ar-H).  $^{13}\text{C}$  NMR (22.5 MHz,  $\text{DMSO-d}_6$ ):  $\delta_{\text{C}}$  20.8, 47.0, 55.6, 55.9, 110.1, 113.8, 119.1, 122.2, 123.1, 125.6, 128.0, 130.8, 131.9, 132.9, 135.6, 136.8, 144.4, 146.7, 152.2, 160.6. *Anal.* Calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2$ : C, 77.09; H, 6.14; N, 7.82%. Found: C, 77.04; H, 6.10; N, 7.78%.

### General procedure for the synthesis of 2-aryl-1H-benzothiazoles 4a-p:

To a solution of *o*-aminobenzenethiol (1 mmol) in MeCN (8 mL) was added the aldehyde **2** (1 mmol). *Trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane **1** (1 mmol) was then added to the mixture followed by the addition of 37% aqueous HCl (3 mmol) and the resulting mixture was stirred for an appropriate time (Table 2). After the completion of the reaction as monitored by TLC (*n*-hexane/EtOAc; 2:1), the reaction was quenched with 3M aqueous solution of  $\text{Na}_2\text{SO}_3$  (1 mL). Then, the reaction mixture was diluted with water (15 mL) and filtered under reduced pressure to leave a solid product **4** which was purified by crystallization from 96% EtOH (Table 2). All the products were characterized by their physical and spectral (IR,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) analysis and compared with the reported data.<sup>36</sup>

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