First Application of Fruit Juice of *Citrus limon* for Facile and Green Synthesis of Bis- and Tris (Indolyl) Methanes in Water

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Abstract

Fruit juice of *Citrus limon* has been utilized for the first time for the facile synthesis of bis- and tris(3-indolyl)methanes in water by the reaction of indoles with aldehydes at room temperature and at 80 °C. The scope of application of the presented method was demonstrated by using the various substituted aromatic, heteroaromatic and aliphatic aldehydes. Ethers, esters, heteroaromatic rings and long chain aliphatic groups also remained unaffected. The presence of electron donating or electron withdrawing groups in the aromatic ring of the aldehydes did not affect the rate of conversion at the experimental conditions. 2-Methylindoles was found to be more reactive than indole. Many advantages for the use of fruit juice of *Citrus limon* as a catalyst in these synthesis, such as, low costs, ease of availability, eco-friendly nature, ease of handling, non-toxicity, high reactivity etc. make fruit juice of *Citrus limon* as a potent catalyst in the synthetic transformation. In conclusion, we have developed a simple, eco-friendly and efficient method for the synthesis of a variety of bis-, and tris(3-indolyl)methane derivatives as biologically active compounds via electrophilic substitution reaction of aldehydes with indoles by fruit juice of *Citrus limon*. The yield was excellent and the protocol was both economic and environmentally friendly.

**Keywords:** Fruit Juice of *Citrus limon*, Homogeneous Catalysis, Indoles, Aldehydes, Bis-, and Tris(indolyl)Methanes

1. Introduction

The importance of bis(indolyl)methanes (BIMs) and its derivatives as potent bioactive intermediates in R & D and pharmaceutical industry cannot be understated. They exhibit a wide range of biological activities such as antibacterial, antitumor and anticancer properties. Tris (indolyl) methanes (TIMs) are found in bacteria, serve as bacterial metabolic and cytotoxic agents (Shiri et al, 2010). Due to the versatile applications of BIMs and TIMs, there is continuous interest in the synthesis of these compounds. Synthetically, the reaction of indole with aldehyde or ketone produces azafulvenium salts that react further with a second indole molecule to form bis(3-indolyl)methanes (Mallik et al, 2007). Numerous methods describing the synthesis of BIMs were reported in the literature employing protic acids and Lewis acids (Shiri et al, 2010). In view of that several synthetic methods for the preparation of BIMs have been reported by using catalysts such as Montmorillonite clay K-10 (Chakrabarty et al, 2004), Cu(BF₄)₂·SiO₂ (Meshram & Patil, 2010), LiClO₄ (Yadav et al, 2001), ZrCl₄ (Zhang et al, 2005), I₂ (Ji et al, 2004), silicotungstic acid (Li & Sun, 2010), NaHSO₄ or Amberlyst-15 (Ramesh et al, 2003) and dysprosium triflate (Mi et al, 2004).

The synthesis of BIMs in aqueous media was reported using aqueous acetic acid (Kamal & Qureshi, 1963) at pH 2.5 at room temperature for 10 days. Subsequent methods for the reaction have been reported in water using alum (Kumar et al, 2009), benzoic acid (Mallik et al, 2012) and in aqueous ethanol using lanthanide triflate (Chen et al,
The use of surfactant or ionic liquid such as sodium dodecyl sulfate (SDS) (Deb & Bhowmik, 2006), oxalic acid/ N-acetyl- N, N-trimethylammonium bromide (CTAB) (Ghorbani-Vaghefi et al, 2010) and ferric dodecyl sulfate [Fe(DS)3] (Wang & Ji, 2008) have also been reported. Most of these methods suffer from various disadvantages such as long reaction periods (Kamal & Qureshi, 1963 and Mallik et al, 2012), use of expensive Lewis acids (Mi et al, 2004) or performed reagents e.g. oxazolines/tetrahydroxazines (Singh et al, 1986), nitrones (Denis et al, 1997), ionic liquid or surfactants (Deb & Bhowmik, 2006; Wang & Ji, 2008 and Ghorbani-Vaghefi et al, 2010) etc., yet furnishing the BIMs in extremely low e.g. 2% (Osawa & Namiki, 1983) or unspecified (Singh & Singh, 1988) yield in some cases. Moreover, some of these are not environmentally friendly, since always an excess of solvent and often toxic or hazardous chemicals are employed. To minimise or completely remove these problems, development of an efficient and versatile method for the preparation of BIMs and TIMs is an important aspect and which is an active going on research and there is a scope for the further improvement towards mild and green reaction conditions and improved yields.

In continuation of this research, we herein report the first example of the synthesis of bis- and tris(3-indolyl)methanes catalyzed by fruit juice of Citrus limon by direct reaction of indoles with aromatic and aliphatic aldehydes in water without the use of any surfactants or ionic liquids. The juice of the lemon contains citric acid which acts as an effective acid catalyst by activating the carbonyl group in water without the use of any surfactants or ionic liquids. Encouraged by the information we studied the effect of reaction of indoles with aromatic and aliphatic aldehydes.

The fruit’s juice was extracted mechanically and centrifuged using micro centrifuge (REMI RM-12C). The clear portion of the juice was used as catalyst for the reactions.

A mixture of indoles (2 mmol) and aldehydes (1 mmol) were taken in fruit juice of Citrus limon-water mixture (10 mL, 2:8 proportion, pH 3) in a round-bottomed flask and stirred at 900 rpm at room temperature for 6 hours in case of indole and 5 hours in case of 2-methylindole. Similarly, the same reactions were also refluxed at 80 °C for 2 hours in case of indole and 1.5 hours in case of 2-methylindole. Upon completion of the reaction, the solid crude products obtained were filtered, washed with water and dried in vacuo. The condensation products were isolated in excellent yields in essentially pure form after crystallization from ethanol.

In conclusion of this research, we herein report the first example of the synthesis of bis- and tris(3-indolyl)methanes catalyzed by fruit juice of Citrus limon by direct reaction of indoles with aromatic and aliphatic aldehydes in water without the use of any surfactants or ionic liquids. The juice of the lemon contains citric acid which acts as the effective acid catalyst by activating the carbonyl group of the aldehydes in this reaction. The lemon juice is highly soluble in water and thus can be removed from the reaction mixture by filtration. Encouraged by the information we studied the effect of fruit juice of Citrus limon on condensation of indoles and aldehydes.

2. Experimental

2.1. Physical Measurements

Melting points were determined on a Kofler block and uncorrected. The infrared (IR) spectra were recorded on Perkin Elmer FT-IR spectrophotometer (spectrum RX 1) and Jasco FT-IR-4200 spectrophotometer as KBr pellets.

1H-NMR spectra were obtained in CDCl3 or DMSO-d6 on a Bruker AV-300 (300 MHz) and Bruker AV-500 (500 MHz) spectrometers using TMS as an internal standard. Mass spectra were acquired on a QTOF micro mass spectrometer. Analytical samples were dried in vacuo at room temperature. The carbon, hydrogen and nitrogen percentages in synthesized products were analyzed by Perkin-Elmer 2400 series II C, H, N analyzers. Thin layer chromatography was carried out on silica gel G.

2.2. Preparation of Fruit Juice of Citrus limon

Fruits of Citrus limon was purchased from the local market. The fruit’s juice was extracted mechanically and centrifuged using micro centrifuge (REMI RM-12C). The clear portion of the juice was used as catalyst for the reactions.

2.3. General Procedure for Synthesis of bis- and tris(3-indolyl)methanes

A mixture of indoles (2 mmol) and aldehydes (1 mmol) were taken in fruit juice of Citrus limon-water mixture (10 mL, 2:8 proportion, pH 3) in a round-bottomed flask and stirred at 900 rpm at room temperature for 6 hours in case of indole and 5 hours in case of 2-methylindole. Similarly, the same reactions were also refluxed at 80 °C for 2 hours in case of indole and 1.5 hours in case of 2-methylindole. Upon completion of the reaction, the solid crude products obtained were filtered, washed with water and dried in vacuo. The condensation products were isolated in excellent yields in essentially pure form after crystallization from ethanol.

2.4. Spectral Data and Elemental Analysis for New Products

3,3’-bis(indolyl)-4-benzoyloxy-3-methoxyphenylmethane (3e): white solid, IR (KBr) v max (cm-1): 3399 and 3366 (N-H), 3057, 2966, 1725 (OCOPh), 1276, 743. 1H-NMR (500MHz, CDCl3) δ H (ppm): 3.68 (3H, s, OMe), 5.90 (1H, s, Ar-CH), 6.67 (2H, s), 6.91 (1H, d, J = 8.1 Hz), 6.99-7.05 (4H, m), 7.17 (2H, t, J = 7.5 Hz), 7.36 (2H, d, J = 8.1 Hz), 7.42 (2H, d, J = 7.8 Hz), 7.49 (2H, t, J = 7.5 Hz), 7.59-7.64 (1H, m), 7.94 (2H, br s, NH), 8.21 (2H, d, J = 8.1 Hz). MS (ES): m/z Calcd for C31H32N2O3 [M+Na]+ 495.17, Found 495.21. Analysis calculated for C31H32N2O3 (472.54): C, 78.80%; H, 5.12%; N, 5.93%; Found: C, 78.69%; H, 5.07%; N, 5.99%.

3,3’-bis(indolyl)-4-benzoyloxyphenylmethane (3g): white crystalline solid, IR (KBr) νmax (cm-1): 3392 (N-H), 3062, 2950, 1723 (OCOPh), 1270, 745. 1H-NMR (500MHz, CDCl3) δ H (ppm): 5.92 (1H, s, Ar-CH), 6.67 (2H, s), 7.02 (2H, t, J = 7.5 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.18 (2H, t, J = 7.5 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.38 (2H, d, J = 8.5 Hz), 7.39 (2H, t, J = 8.1 Hz), 7.50 (2H, t, J = 7.8 Hz), 7.62

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(1H, m), 7.95 (2H, br s, NH), 8.19 (2H, d, J = 9.0 Hz). HRMS (ES'): m/z Calcd for C$_{30}$H$_{22}$N$_2$O$_2$ [M+Na]$^+$ 465.1578, Found 465.1578. Analysis Calculated for C$_{30}$H$_{22}$N$_2$O$_2$ (442.52): C, 81.43%; H, 5.01%; N, 6.33%; Found: C, 80.93%; H, 4.90%; N, 6.39.

3,3'-bis(2-methylindolyl)-4-benzoyloxy-3-methoxynaphthalene (3t): white solid, IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3401 and 3375 (N-H), 3057, 2933, 1725 (OCOPh), 1275, 743.

$^1$H-NMR 300MHz, (DMSO-d$_6$) $\delta$H (ppm): 2.50 (6H, s, Me), 3.55 (3H, s, OMe), 5.97 (1H, s, Ar-CH), 6.76-6.69 (3H, m), 6.92-6.87 (4H, m), 7.10 (2H, d, J = 9.1 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.59 (2H, t, J = 7.5 Hz), 7.76-7.71 (1H, m), 8.11 (2H, d, J = 7.2 Hz), 10.76 (2H, br s, NH). MS (ES$^+$): m/z Calcd for C$_{33}$H$_{28}$N$_2$O$_3$ [M+Na]$^+$ 523.20, Found 523.26. Analysis Calculated for C$_{33}$H$_{28}$N$_2$O$_3$ (500.60): C, 79.18%; H, 5.64%; N, 5.60%; Found: C, 79.56%; H, 5.58%; N, 5.63.

3,3'-bis(2-methylindolyl)-n-propylmethane (3u): white solid, IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3385 (N-H), 3055, 2955, 1458, 1302, 745.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$H (ppm): 0.95 (3H, t, J = 7.5 Hz), 1.36-1.44 (2H, m), 2.34 (6H, s, Me), 2.38-2.47 (2H, m), 4.41 (1H, t, J = 7.8 Hz, Ar-CH), 6.97 (2H, t, J = 7.5 Hz), 7.04 (2H, t, J = 7.5 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.62 (2H, d, J = 7.8 Hz), 7.64 (2H, br s, NH). MS (ES$^+$): m/z Calcd for C$_{22}$H$_{24}$N$_2$ [M+Na]$^+$ 339.18, Found 339.23. Analysis Calculated for C$_{22}$H$_{24}$N$_2$ (316.45): C, 83.50%; H, 7.64%; N, 8.85%; Found: C, 83.41%; H, 7.59%; N, 8.97.

3. Results and Discussion

A facile and clean route using fruit juice of *Citrus limon* as a mild and highly efficient acid catalyst for the comparative synthesis of bis(3-indolyl) methanes 3 at room temperature and 80 °C were described in Scheme 1.

To achieve the best results for this reaction (Scheme 1) we have studied the synthesis of bis(3-indolyl) phenylmethan-
Table 2. Synthesis of bis- and tris(3-indolyl)methanes (3) by Condensation of Indoles with Aldehydes Catalyzed by Fruit Juice of *Citrus limon*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^1</th>
<th>Product (3)</th>
<th>Reaction Condition</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>M. P. (°C) (Lit. Value)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>C_6H_5</td>
<td>3a</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>82 95</td>
<td>87-89 (88-90)</td>
<td>Yadav et al, 2001</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>4-MeO-C_6H_4</td>
<td>3b</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>78 85</td>
<td>185-186 (187-189)</td>
<td>Ji et al, 2004</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>4-Cl-C_6H_4</td>
<td>3c</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>75 80</td>
<td>93-95 (94-96)</td>
<td>Ji et al, 2004</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>4-OH-3-MeO-C_6H_4</td>
<td>3d</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>70 88</td>
<td>125 (126-127)</td>
<td>Deb &amp; Bhuyan, 2006</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>4-OCOC_6H_4-3-MeO-C_6H_4</td>
<td>3e</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>72 95</td>
<td>240-241</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>4-OH-C_6H_4</td>
<td>3f</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>70 85</td>
<td>121 (120-122)</td>
<td>Zhang et al, 2005</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>4-OCOC_6H_4-3-MeO-C_6H_4</td>
<td>3g</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>78 92</td>
<td>218-220</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>H</td>
<td>4-Cl-C_6H_4</td>
<td>3h</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>72 88</td>
<td>73-74 (74-76)</td>
<td>Meshram &amp; Patil, 2010</td>
</tr>
<tr>
<td>i</td>
<td>H</td>
<td>4-Br-C_6H_4</td>
<td>3i</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>70 88</td>
<td>109-111 (108-110)</td>
<td>Mallik et al, 2012</td>
</tr>
<tr>
<td>j</td>
<td>H</td>
<td>4-NO_2-C_6H_4</td>
<td>3j</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>85 92</td>
<td>217-220 (219-222)</td>
<td>Meshram &amp; Patil, 2010</td>
</tr>
<tr>
<td>k</td>
<td>H</td>
<td>4-NMe_2-C_6H_4</td>
<td>3k</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>70 78</td>
<td>208-210 (210-212)</td>
<td>Ghorbani-Vaghei et al, 2010</td>
</tr>
<tr>
<td>l</td>
<td>H</td>
<td>2-furyl</td>
<td>3l</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>70 85</td>
<td>321-323 (320-322)</td>
<td>Zhang et al, 2005</td>
</tr>
<tr>
<td>m</td>
<td>H</td>
<td>n-C_3H_7</td>
<td>3m</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>75 88</td>
<td>107 (106-108)</td>
<td>Li &amp; Sun, 2010</td>
</tr>
<tr>
<td>n</td>
<td>H</td>
<td>n-C_6H_{11}</td>
<td>3n</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>65 80</td>
<td>67-69 (68-70)</td>
<td>Yadav et al, 2001</td>
</tr>
<tr>
<td>o</td>
<td>Me</td>
<td>C_6H_5</td>
<td>3o</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>85 88</td>
<td>245-246 (247-248)</td>
<td>Deb &amp; Bhuyan, 2006</td>
</tr>
<tr>
<td>p</td>
<td>Me</td>
<td>4-MeO-C_6H_4</td>
<td>3p</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>75 90</td>
<td>98-99 (98-100)</td>
<td>Yadav et al, 2001</td>
</tr>
<tr>
<td>q</td>
<td>Me</td>
<td>4-Me-C_6H_4</td>
<td>3q</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>68 92</td>
<td>173-174 (174-175)</td>
<td>Deb &amp; Bhuyan, 2006</td>
</tr>
<tr>
<td>r</td>
<td>Me</td>
<td>3,4-</td>
<td>3r</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>77 88</td>
<td>225-227 (226-228)</td>
<td>Mallik et al, 2012</td>
</tr>
<tr>
<td>s</td>
<td>Me</td>
<td>4-Cl-C_6H_4</td>
<td>3s</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>80 90</td>
<td>236-238 (238-239)</td>
<td>Mallik et al, 2012</td>
</tr>
<tr>
<td>t</td>
<td>Me</td>
<td>4-OCOC_6H_4-3-MeO-C_6H_4</td>
<td>3t</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>80 93</td>
<td>274-275</td>
<td></td>
</tr>
<tr>
<td>u</td>
<td>Me</td>
<td>n-C_3H_7</td>
<td>3u</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>78 82</td>
<td>129-130</td>
<td></td>
</tr>
<tr>
<td>v</td>
<td>H</td>
<td>3-indolyl</td>
<td>3v</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>6 2</td>
<td>65 80</td>
<td>249-251</td>
<td>Ramesh et al, 2003</td>
</tr>
<tr>
<td>w</td>
<td>Me</td>
<td>3-indolyl</td>
<td>3w</td>
<td>(i) H_2O, rt (ii) H_2O, 80 °C</td>
<td>5 1.5</td>
<td>75 83</td>
<td>268-269</td>
<td>Ramesh et al, 2003</td>
</tr>
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ction with indoles under the above reaction conditions to smoothly afford a wide range of substituted bis(3-indolyl) methanes in good to excellent yields. It was found that on increasing the temperature to 80 °C, the reaction time was reduced to 2 hours in case of indole and 1.5 hours in case of 2-methylindole. The presence of electron donating or electron withdrawing group in the aromatic ring of the aldehydes did not affect the rate of conversion under the present experimental conditions. The ether (entries b, d, e, p, r, and t) and ester (entries e, g and t) linkages present in the aldehydes remain unaffected. The procedure was successfully applied for heteroaromatic aldehyde (entry l) and the corresponding BIMs was obtained in 85% yield. 2-Methylindole (entries o-u) was found to be more reactive than indole (entries a-n) giving products in excellent yield in shorter reaction times.

The reaction was further explored for the synthesis of tris(3-indolyl)methanes i.e. 3v and 3w by the condensation of 3-formylindole with two equivalents of indoles under similar conditions in high yields (Scheme 1, Table 2). The structures of the known products were settled by the comparison of 1H-NMR and melting points with their literature data and the structures for the unknown products were settled from their analytical and spectral (IR, 1H-NMR and Mass) data.

When a mixture of 4-methoxybenzaldehyde and acetophenone was treated with indole in presence of lemon juice at room temperature and 80 °C, the method proved to be chemoselective produced only bis(3-indolyl)-4-methoxyphenylmethane, while acetophenone did not give the corresponding product. In case of an equimolar mixture of aryl aldehyde and aliphatic aldehyde, the aryl aldehyde was chemoselectively converted to the corresponding bis(3-indolyl)methane (major) (Scheme 2). The reaction was clean and the products were obtained in high yields without the formation of any by-products. At room temperature the yields were 65-85% and the yields of the products at 80 °C were 80-95%. The purity of the products were about 97% (Table 2).

Our findings reflect the wide applicability and usefulness of the method. Some previously reported data on reaction conditions and the yield of the product for preparation of bis(3-indolyl)phenylmethane 3a (Table 2, entry a) were compared with our results (Table 3). As one can see our results show a very good comparability with previously reported data in order to yields and reaction times.

4. Conclusions

The work constitutes the first report of a simple and efficient synthesis of bis- and tris(3-indolyl) methanes using easily accessible fruit juice of Citrus limon as catalysts. The method is green and uses water as the most eco-compatible reaction medium. Catalyst is inexpensive giving high yield of the product with good purity without column chromatographic separation. Complete elimination of the toxic solvents, reagents, and inorganic support were also achieved. Lastly, it has a general applicability accommodating a variety of substitution patterns and the products 3e, 3g, 3t and 3u are new compounds, and may have potential biological activities.

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