

Microwave-assisted eco-friendly synthesis of bis-, tris(indolyl)methanes and synthesis of di-bis(indolyl)methanes catalyzed by fruit juice of *Citrus limon* under solvent-free conditions

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Abstract: Microwave-assisted efficient and eco-friendly synthesis of bis-, tris(indolyl)methanes and di-bis(indolyl)methanes by the reaction of indoles with aldehydes in presence of fruit juice of *Citrus limon* as catalyst under solvent-free conditions is reported. The advantages of the protocol are the use of green and inexpensive catalyst, commercially available precursors, simple work-up procedures, high yields and short reaction times.

Keywords: Bis-, tris-, and tetra(indolyl)methanes, Microwave irradiation, Fruit juice of *Citrus limon*, Green and inexpensive acid catalyst, Eco-friendly

I. Introduction

Many synthetic chemists have made a great deal of effort to design sustainable and clean procedures to replace the classical synthetic methods [1]. Application of microwave irradiation chemistry to enhance the efficiency and/or selectivity of organic reactions is one of the well-known challenges [2]. Microwave-assisted organic synthesis exploits a variety of factors such as milder and more efficient conditions, high yields and shorter reaction times, energy conservation, formation of purer products, waste minimization and easier manipulation. Microwave irradiation is well-known to promote the synthesis of a variety of compounds [3-4], where chemical reactions are accelerated because of selective absorption of microwave by polar molecules. Recently, the coupling of microwave irradiation with polar organic molecules under solvent-free conditions has received notable attention [4]. A literature survey reveals example of specific reactions, which do not occur under conventional conditional heating, but could be possible by microwave irradiation [5].

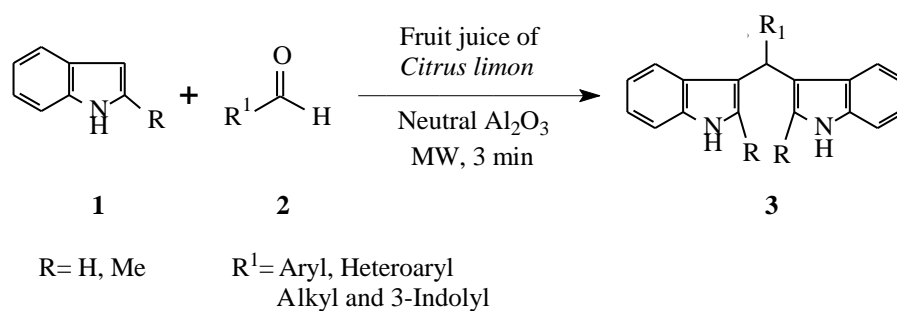
Today, there is a great demand for green and inexpensive acids instead of conventional mineral acids such as HF, H₂SO₄ and HCl in chemical processes. Mineral acids are corrosive and hazardous catalysts [6]. Fruit juice of *Citrus limon* contains citric acid which could be acts as an effective acid catalyst by activating the carbonyl group of the aldehydes in organic reactions. Easy preparation and handling, separation and work-up processes, non-hazardous nature and easier waste disposal are among the most common characteristics that makes it a green catalysts.

Indoles and their derivatives are known as an important class of heterocyclic compounds and bioactive intermediates in R & D and pharmaceutical industry [7]. Bis(indolyl)methanes (BIMs) exhibit a wide range of biological activities such as antimicrobial and antifungal [8], antibacterial [9], analgesic and anti-inflammatory [10], growth promoting [11], antitumor [12] and anticancer [13] activities. Recently, Maciejewska *et al.* [14] used DNA-based electrochemical biosensors to demonstrate that bis(5-methoxy-3-indolyl)methane considerably reduces the growth of cancer cell lines such as HOP-92 (lung), A498 (renal), and MDAMB-231/ITCC (breast). Tris(indolyl)methanes (TIMs) found in bacteria [15].serve as bacterial metabolic [16] and cytotoxic [17] agents. Due to the versatile applications of BIMs and TIMs, there is continuous interest in the synthesis of these compounds [18-19]. 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 [20]. Numerous methods describing the synthesis of bis(indolyl)methanes were reported in the literature employing protic acids [21] include silica sulfuric acid [22], silica supported NaHSO₄/amberlyst-15 [23] and Lewis acids such as iodine [24], lithium perchlorate [25], cupric fluoroborate [26] and silicotungstic acid [27]. Recently, benzoic acid [28] in water, sodium dodecylsulfate (SDS) [29] as surfactant in water, oxalic acid combination with *N*-acetyl-*N,N,N*-trimethylammonium bromide (CTAB) [30] as surfactant in water, metal triflate in ionic liquid [31], Fe(III) salts in ionic liquid [32] and ionic liquid [33] were reported to be efficient for this transformation. Although, ionic liquids are reusable but ionic liquid and surfactants are very expensive. However, there are still some drawback in the catalytic system including the requirement of large [34-35], or stoichiometric amount of catalysts [19,36], long reaction times [28], [34-35] low yields of products [19] and drastic reaction condition for catalyst preparation [37].

In continuation of this research, I herein report the first example of the synthesis of bis-, tris(indolyl)methanes and di-bis(indolyl)methanes in presence of fruit juice of *Citrus limon* a green, inexpensive and easily available acid catalyst by direct reaction of indoles with aromatic and aliphatic aldehydes using microwave irradiation under solvent-free conditions (Scheme 1).

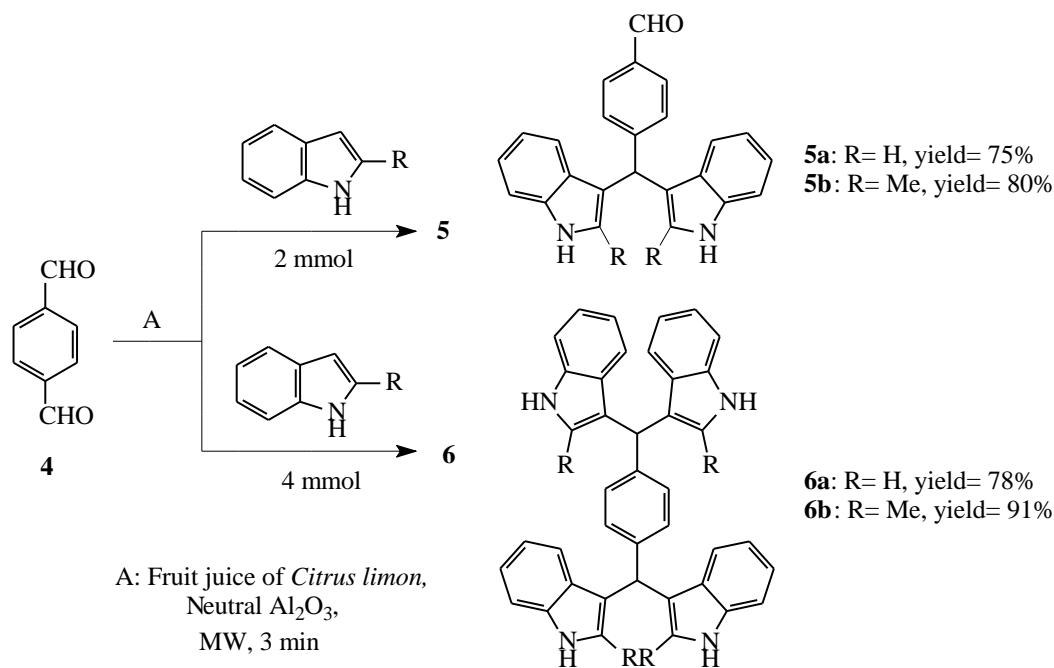
II. Results And Discussion

In the present article, 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** under microwave irradiation condition were described (Scheme 1). I have found that indole / 2-methylindole (2 mmol) when reacted with various aldehydes (1 mmol) in presence of fruit juice of *Citrus limon* in neutral alumina under microwave irradiation produces bis(3-indolyl)methanes (**3a-x**) in high yields (Scheme 1, Table 1). When 3-formylindole was used as a aldehydes the corresponding tris(3-indolyl)methanes (**3y** and **z**) are formed in similar reaction conditions. 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.



Scheme 1

The scope of application of the presented method is demonstrated by using the various substituted aromatic and aliphatic aldehydes to react with indoles. The procedure was successfully applied for heteroaromatic aldehyde (entry n) and the corresponding BIMs was obtained in 85% yield. The electronic nature of the substituents in the aromatic ring did not show any noticeable effect on this conversion. The long-chain aliphatic aldehydes (entries o, p and x) also worked well to form the products in high yields. The ether (entries b, d, e and r) and esters linkages (entries g, h and v) present in the aldehydes were unaffected. The activity of indole and 2-methylindole was found to be almost similar towards the reaction. The results are summarized in (Table 1).



Scheme 2

Interestingly, when I used terephthalaldehyde (**4**) and indoles in 1:2 ratio, *p*-bis-indolylmethane benzaldehydes (**5a** [38] and **5b**) were obtained in good yields. When 4 molar equivalents of indoles were used, *p*-di(bis-indolylmethane)benzenes (**6**) were obtained in 78% and 91% yields of **6a** [38] and **6b** respectively (Scheme 2).

Table 1. Microwave-assisted synthesis of bis- and tris(3-indolyl)methanes (**3**) catalyzed by fruit juice of *Citrus limon* under solvent-free conditions^a.

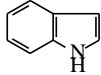

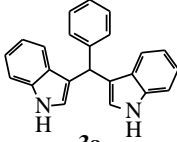
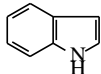
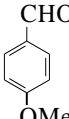
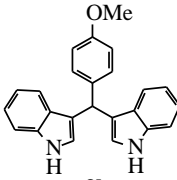
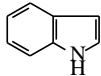
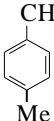
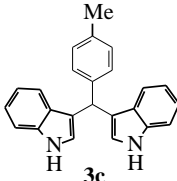
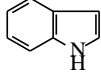
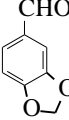
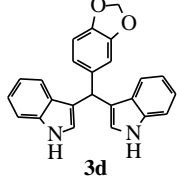
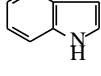
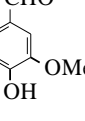
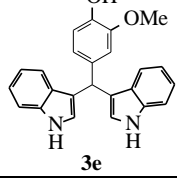
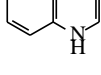
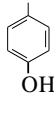
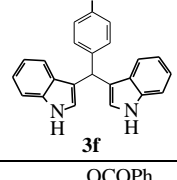
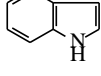
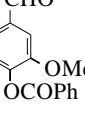
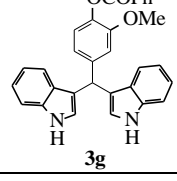
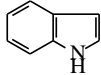
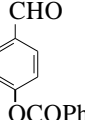
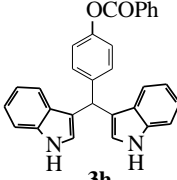
Entry	Indole (1)	Aldehyde (2)	Product (3)	Yield (%) ^b	M.p. (°C) (Lit. Value) ^d
a			 3a	86	87-89 (88-90) ²⁵
b			 3b	85	185-186 (185-187) ^{27b}
c			 3c	80	93-95 (94-96) ²⁴
d			 3d	85	96-97 (97-99) ²⁵
e			 3e	80	125 (126-127) ²⁹
f			 3f	82	121 (120-121) ³⁰
g			 3g	90	240-241
h			 3h	95	218-220

Table 1. Continued

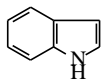
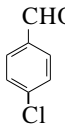
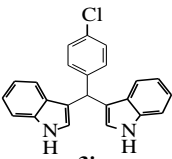
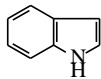
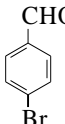
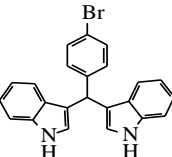
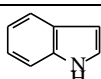
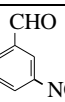
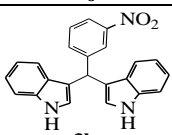
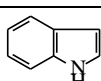
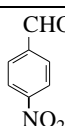
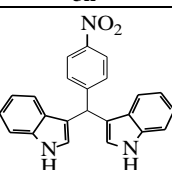
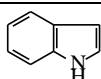
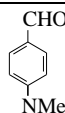
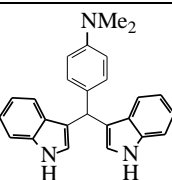
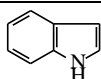

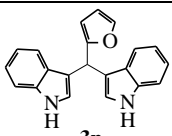
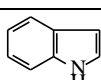

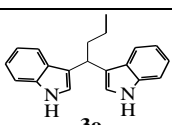
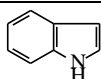

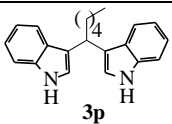
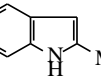

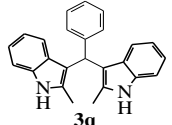
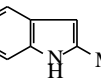
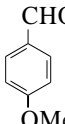
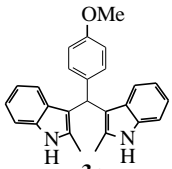
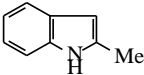
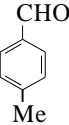
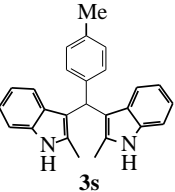
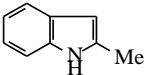
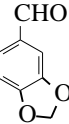
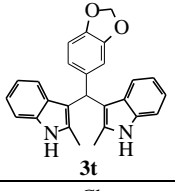
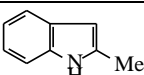
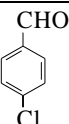
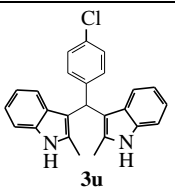
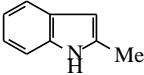
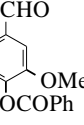
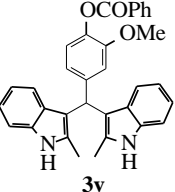
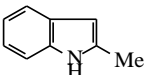
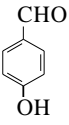
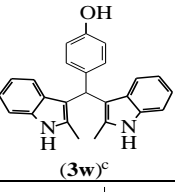
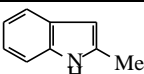
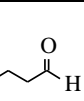
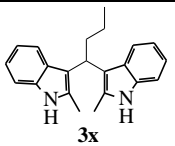

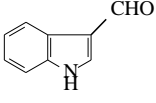
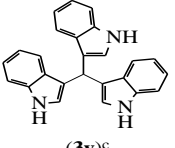
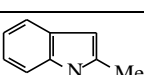
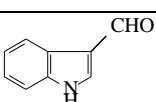
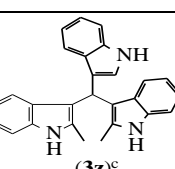
Entry	Indole (1)	Aldehyde (2)	Product (3)	Yield (%) ^b	M.p. (°C) (Lit. Value) ^d
i				88	73-74 (74-76) ²⁶
j				76	109-111 (110-112) ³⁰
k				95	220 (220-222) ^{27b}
l				95	217-220 (219-222) ²⁶
m				75	208-210 (210-212) ³⁰
n				85	321-323 (322-324) ³⁰
o				80	107 (106-108) ^{27a}
p				75	67-69 (68-70) ²⁵
q				85	245-246 (247-248) ²⁹
r				80	98-99 (98-100) ²⁵

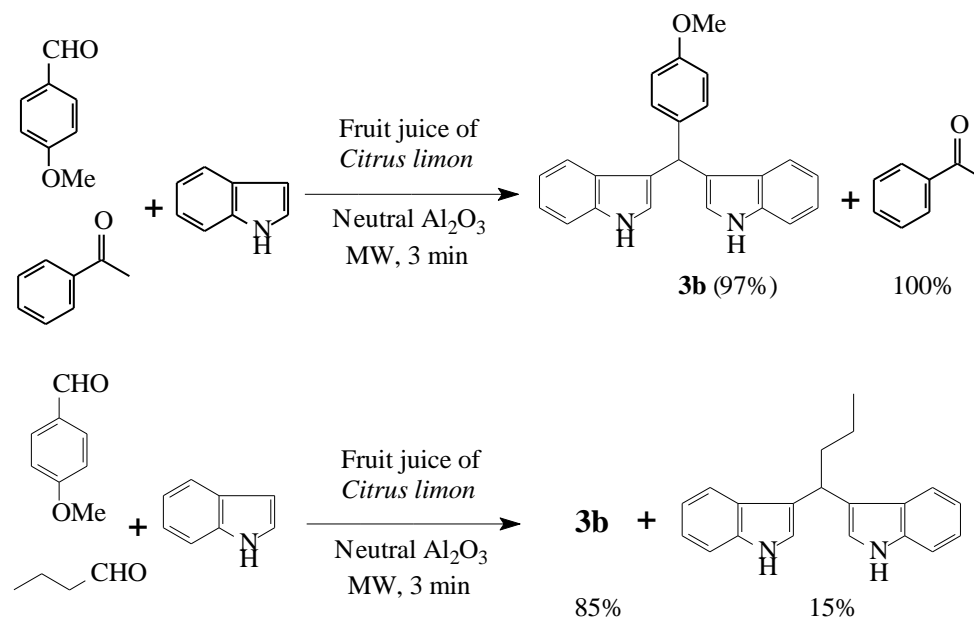
Table 1. Continued

Entry	Indole (1)	Aldehyde (2)	Product (3)	Yield (%) ^b	M.p. (°C) (Lit. Value) ^d
s				90	173-174 (174-175) ²⁹
t				85	225-227 (226-228) ²⁸
u				92	236-238 (238-239) ²⁸
v				90	274-275
w				75	241-243
x				76	129-130
y				82	249-251
z				80	268-269

^a Reaction time 3 min; ^b Isolated yield; ^c Known compound ref. 23; ^d References for melting point.

This method is also highly chemoselective for aryl aldehydes in presence of ketones and aliphatic aldehydes. For example, when 1:1 mixture of 4-methoxybenzaldehyde and acetophenone was allowed to react with indole in presence of lemon juice in neutral alumina under microwave irradiation, it was found that only 3,3'-bis(indolyl)-4-methoxyphenylmethane (**3b**) was obtained, while acetophenone did not give the corresponding product under this reaction condition. Also, in an equimolar mixture aryl aldehyde and aliphatic aldehyde, it was found that aryl aldehyde were chemoselectively converted to the corresponding bis(3-indolyl)methane, but the

aliphatic ones converted slightly (Scheme 3). The reaction was clean and the products were obtained in high yields with out the formation of any by-products.



Scheme 3

III. Experimental

3.1. Chemicals and Apparatus

All the chemicals used in the present study are of analytical grade and were obtained from local suppliers. Melting points were determined on a Kofler block and uncorrected. 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 CDCl_3 or DMSO-d_6 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. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. Column chromatography were performed on silica gel (100-200 mesh) using petroleum ether (60-80°C)-ethyl acetate mixture as eluents. TLC was carried out on silica gel G.

3.2. Preparation of fruit juice from the fruits 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.

3.3. General procedure for synthesis of bis-, tris-, and tetraindolyl compounds

A mixture of indoles **1** (2 mmol), aldehydes **2** (1 mmol), fruit juice of *Citrus limon* (1 ml) and neutral alumina (Al_2O_3 , 1.5 gm) were grinded with mortar and pestle and it was dried. The solid mixture was irradiated under a microwave (LG, MH-4048GW, 480 W, 3 min). After completion of the reaction, the reaction mixture was diluted with water and then extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrate under reduced pressure. The obtained crude product was purified by rapid column chromatography on silica gel using petroleum ether-ethyl acetate mixtures to obtained pure bis- and tris (3-indolyl)methanes **3** (Table 1) and *p*-3,3'-bis(indolyl)methane benzaldehydes (**5**). Tetraindolyl compounds **6** were obtained in similar reaction conditions using 4 molar proportions of indoles. Majority of the compounds were known compounds and characterized from the reported melting points (referred in Table 1) and ^1H NMR data and compounds **3g-h**, **3v**, **3x**, **5b** and **6b** were unknown. The unknown products were characterized from their analytical and spectral (IR, ^1H NMR, ^{13}C and mass) data.

1.4. Analytical and Spectral data of unknown products

3,3'-Bis(indolyl)-4-benzoyloxy-3-methoxyphenylmethane **3g** (Table 1, entry g). White solid. m.p.: 240-241 °C; IR (KBr) ν_{max} 3399 and 3366 (N-H), 3057, 2966, 1725 (OCOPh), 1276, 743 cm^{-1} ; ^1H NMR (300MHz,

CDCl₃): δ 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 (ESI) *m/z*: Calcd for C₃₁H₂₄N₂O₃ [M+Na]⁺ 495.17, Found 495.21. Anal. Calcd for C₃₁H₂₄N₂O₃ (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 3h (Table 1, entry h). White crystalline solid. m.p.: 218-220 °C; IR (KBr)_{v_{max}} 3392 (N-H), 3062, 2950, 1723 (OCOPh), 1270, 745 cm⁻¹; ¹H NMR (500MHz, CDCl₃): δ 5.92 (1H, s, Ar-CH), 6.67 (2H, s), 7.02 (2H, t, *J* = 7.5 Hz), 7.13 (2H, d, *J* = .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 (1H, m), 7.95 (2H, br s, NH), 8.19 (2H, d, *J* = 9.0 Hz). HRMS (ESI) *m/z*: Calcd for C₃₀H₂₂N₂O₂ [M+Na]⁺ 465.1578, Found 465.1578. Anal. Calcd for C₃₀H₂₂N₂O₂ (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-methoxyphenylmethane 3v (Table 1, entry v). White solid. m.p.: 274-275 °C. IR (KBr)_{v_{max}} 3401 and 3375 (N-H), 3057, 2933, 1725 (OCOPh), 1275, 743 cm⁻¹; ¹H NMR (300MHz, DMSO-d₆): δ 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 (ESI) *m/z*: Calcd for C₃₃H₂₈N₂O₃ [M+Na]⁺ 523.20, Found 523.26. Anal. Calcd for C₃₃H₂₈N₂O₃ (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 3x (Table 1, entry x). White solid. m.p. 129-130 °C.: IR _{v_{max}} (KBr) : 3385 (N-H), 3055, 2955, 1458, 1302, 745 cm⁻¹; ¹H NMR (300MHz, CDCl₃): δ 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 (ESI) *m/z*: Calcd for C₂₂H₂₄N₂ [M+Na]⁺ 339.18, Found 339.23. Anal. Calcd for C₂₂H₂₄N₂ (316.45): C, 83.50; H, 7.64; N, 8.85%. Found: C, 83.41; H, 7.59; N, 8.97%.

p-3,3'-Bis(2-methylindolyl)methane benzaldehyde 5b Pink solid. m.p.: 232-234 °C. ¹H NMR (300MHz, DMSO-d₆): δ 2.08 (6H, s, CH₃), 6.01 (1H, s, Ar-CH), 6.67 (2H, t, *J* = 7.5 Hz), 6.79 (2H, d, *J* = 7.5 Hz), 6.89 (2H, t, *J* = 7.8 Hz), 7.22 (2H, d, *J* = 7.8 Hz), 7.39 (2H, d, *J* = 8.1 Hz), 7.81 (2H, d, *J* = 8.1 Hz), 9.96 (1H, s, CHO), 10.82 (2H, br s, NH); MS (ESI) *m/z*: Calcd for C₂₆H₂₂N₂O [M-H]⁺ 377.17, Found 377.23. Anal. Calcd for C₂₆H₂₂N₂O (378.47): C, 82.52; H, 5.86; N, 7.40%. Found: C, 82.62; H, 5.97; N, 7.13%.

p-Di[3,3'-bis(2-methylindolyl)methane]benzene 6b Red solid. m.p.: 280-282 °C.: IR _{v_{max}} (KBr): 3390 (N-H), 3055, 2944, 1454, 1300, 746 cm⁻¹; ¹H NMR (300MHz, DMSO-d₆): δ 2.09 (12H, s, CH₃), 5.87 (2H, s), 6.67 (4H, t, *J* = 7.5 Hz), 6.88 (2H, t, *J* = 8.7 Hz), 6.90 (4H, d, *J* = 8.4 Hz), 7.05 (4H, s), 7.18 (4H, d, *J* = 7.8 Hz), 10.71 (4H, br s, NH). ¹³C NMR (75MHz, DMSO-d₆): δ 12.05 (CH₃), 38.26 (Ar-CH), 110.29, 111.89, 112.33, 117.84, 118.67, 19.49, 128.29, 131.99, 135.05, 141.52; MS (ESI) *m/z*: Calcd for C₄₄H₃₈N₄ [M-H]⁺ 621.30, Found 621.25. Anal. Calcd for C₄₄H₃₈N₄ (622.80): C, 84.85; H, 6.15; N, 9.00. Found: C, 84.71; H, 6.27; N, 8.89.

IV. Conclusions

Fruit juice of *Citrus limon* promotes the condensation of indoles and aldehydes using microwave irradiation under solvent-free conditions. The notable advantages of this procedure are: (a) reasonably good yield; (b) shorter reaction times; (c) mild conditions; (d) in tune with green synthesis avoiding toxic reagents; (e) It has a general applicability accommodating a variety of substitution patterns and the products **3g-h**, **3v**, **3x**, **5b** and **6b** are new compounds and may have potential biological activities. I believe this procedure will play an important role in the preparation of nitrogen heterocyclic derivatives.

Acknowledgements

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