

New Greener Alternative for Biocondensation of Aldehydes and Indoles Using Lemon Juice: Formation of Bis-, Tris-, and Tetraindoles

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ABSTRACT

This work presents a new greener alternative for biocondensation of aldehydes and indoles for the synthesis of bis- and tris(indolyl)methanes catalyzed by lemon juice (*Citrus limon*) in good yields under ultrasound irradiation in aqueous ethanol. Various substituted aldehydes with indoles under this reaction condition are elucidated. Also, tetraindolyl compounds were prepared using terephthalaldehyde by following the same protocol. This method is an environmentally benign, efficient reaction, which requires shorter reaction time and simple experimental and work-up procedures.

Keywords: *Citrus limon* Juice; Biocondensation; Aldehydes; Indoles; Aqueous Ethanol; Sonication; Bis-; Tris-; Tetraindoles

1. Introduction

Indoles and their derivatives are known as an important class of heterocyclic compounds and bioactive intermediates in R & D and pharmaceutical industry [1]. Bis(indolyl)methanes (BIMs) and tris(indolyl)methanes (TIMs) exhibit a wide range of biological activities [2]. Tetraindolyl compounds such as 1,4-di[bis(3-indolyl)methyl]benzene are used in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [3]. Due to the versatile applications of BIMs and TIMs, there is continuous interest in the synthesis of these compounds [4]. 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 [5]. Different protic acids [6,7] including silica sulfuric acid [8], silica supported NaHSO₄ and amberlyst-15 [9], silica supported KaHSO₄ [10] and Lewis acids [2,11-13] are known to catalyze this reaction. The protic acids (e.g., HCl and H₂SO₄) and Lewis acids (e.g., BBr₃ and BF₃) which are generally used are hazardous and difficult to handle and remove from the reaction mixture. Some of the reported catalysts may decompose the indoles or disturb the functionalities. Several catalysts are not also readily available or expensive. Recently, the reactions were carried in acetonitrile in presence of many kind of catalyst, such as InCl₃, In(OTf)₃ [14], I₂

[15], trichloro-1,3,5-triazine (TCT) [16], PPh₃·HClO₄ [17]. However, the acetonitrile is not an environmentally friendly solvent and therefore environmentally friendly and cheaper solvent is desirable.

Organic reactions in aqueous media or aqueous ethanol media have attracted much attention because both water and ethanol are considerably safe, non-toxic, environmentally-friendly, and cheap compared to organic solvents [18]. The synthesis of bis(indolyl)methanes in water was first reported using acetic acid [19] at pH 2.5 at room temperature for 10 days. Subsequent methods for the reaction in water have been reported using alum [20], benzoic acid [21], in aqueous ethanol using lanthanide triflate [22], zirconium oxychloride [23]. The use of surfactant or ionic liquid such as sodium dodecyl sulfate (SDS) [24], oxalic acid/*N*-acetyl-*N,N,N*-trimethylammonium bromide (CTAB) [25] and ferric dodesyl sulfonate [Fe(DS)₃] [26] has also been reported. Most of these methods suffer from various disadvantages such as long reaction periods, harsh experimental procedure and surfactants or ionic liquid that are expensive.

Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, the ultrasound procedure is more convenient and can be carried out in higher yield, shorter reaction time or mild conditions [27,28]. Zeng, *et al.* [29]

have reported synthesis of BIMS catalyzed by ceric ammonium nitrate (CAN) under ultrasound irradiation. Subsequently, other ultrasound irradiation methods using aminosulfonic acid [30], Meldrum's acid [31], silicotungstic acid [32] and acrylonitrile butadiene styrene (ABS) [33] were also reported. However, the catalysts used are hazardous, expensive and not easily available.

Among the challenges for chemists including discovery and development of inexpensive, non-hazardous and simple environmentally safe chemical processes for selective synthesis by identifying alternative reaction conditions and solvents that much improved selectivity, energy conservation and even less hazardous waste generation are not desirable and inherently safer chemical products. Therefore, to address depletion of natural resources and preservation of ecosystem is just urgent to develop so called "greener technologies" to make chemical agents for well being of human health. Due to acidic nature (pH = 3.0), aqueous *Citrus limon* juice as a natural catalyst has been found to be a suitable replacement for various homogeneous acid catalysts.

2. Results and Discussion

In continuation of our research and interest in the development of novel synthetic methodologies using fruit juice [34,35], herein we would like to report an one-pot two component synthesis of bis-, tris-, and tetra-(indolyl)methanes using *Citrus limon* juice as natural catalyst. The biocondensation between indoles and aldehydes takes place smoothly in presence of *Citrus limon* juice in aqueous ethanol under ultrasound irradiation without the use of any surfactant. The juice of the *Citrus limon* contains citric acid (5% - 8%) and ascorbic acid are the main components of the juice which acts as the effective acid catalyst by activating the carbonyl group of the aldehydes in this reaction. The juice is highly soluble in water and thus acts as a homogeneous catalysis on biocondensation of indoles and aldehydes in aqueous ethanol system. Ethanol is also a green solvent used along with water because aldehydes and indoles is less soluble in water only.

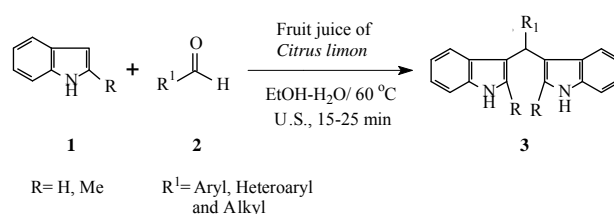
We have recently observed that *Citrus limon* juice acts a homogeneous acid catalyst for the electrophilic substitution reaction of indoles with aldehydes (Scheme 1). We have found that indole or 2-methylindole (2 mmol) when reacted with various aldehydes (1 mmol) in presence of *Citrus limon* juice (2 ml) in ethanol-water mixture (8 ml, ratio: 3:5) at 60°C under ultrasound irradiation produces bis(3-indolyl)methanes (3a-x) in high yields (Scheme 1, Table 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 proce-

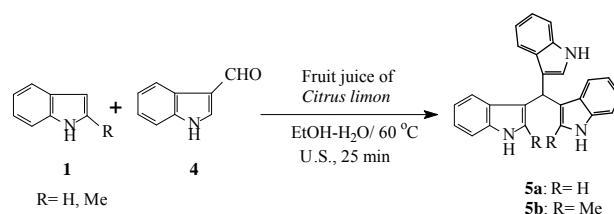
cedure was successfully applied for heteroaromatic aldehyde (entry n) and the corresponding BIMs was obtained in 85% yield. The electronic nature of the substituents in the aromatic ring did not show any noticeable effect on this conversion. The long-chain aliphatic aldehydes (entries o, p and x) also worked well to form the products in high yields. The ether (entries b, d, e, f, r, t and v) and esters linkages (entries f, 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 reaction was further explored for the synthesis of tris(3-indolyl)methanes by the condensation of an heteroaromatic aldehyde *i.e.* 3-formylindole with two equivalents of indoles under similar condition at 60°C. The products 5a and 5b were produced in 60% and 75% yields respectively (Scheme 2, Table 2).

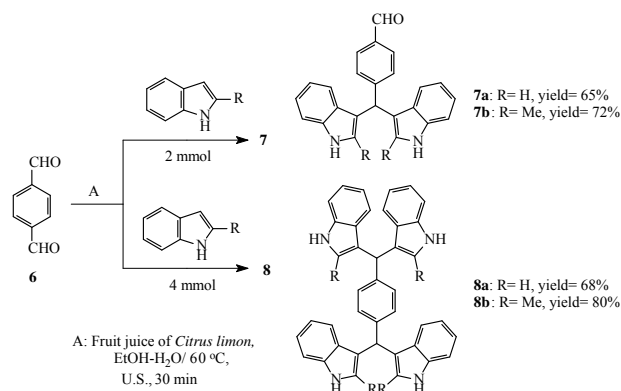
Interestingly, *Citrus limon* juice was effectively used for the synthesis of di-bis(indolyl)methanes from indoles and terephthalaldehyde (6) (Scheme 3, Table 2). The reaction of 2 equivalents of indoles with 1 equivalent of terephthalaldehyde proceeded successfully to give *p*-



Scheme 1. Synthesis of bis(3-indolyl)methanes.



























Scheme 2. Synthesis of tris(3-indolyl)methanes.



Scheme 3. Synthesis of *p*-bis(indolyl)methyl benzaldehydes and tetraindoles.

Table 1. Synthesis of bis(3-indolyl)methanes (3) from the biocondensation of indoles (1) with aldehydes (2) using fruit juice of *Citrus limon* under ultrasound irradiation^a.

Entry	R (1)	R ¹ (2)	Product (3)	Time (min)	Yield (%) ^b	M.p. (°C) (Lit. Value)	References
a	H		3a	15	80	86 - 88 (88 - 90)	13
b	H		3b	20	75	183 - 184 (185 - 187)	32
c	H		3c	18	80	93 - 95 (94 - 96)	15
d	H		3d	20	82	95 - 96 (97 - 99)	13
e	H		3e	25	72	125 (126 - 127)	24
f	H		3f	17	85	238 - 240 (240 - 241)	34
g	H		3g	23	80	121 (120 - 121)	25
h	H		3h	15	88	216 (218 - 220)	34
i	H		3i	15	78	73 - 74 (74 - 76)	12
j	H		3j	20	70	108 - 111 (110 - 112)	25
k	H		3k	15	90	220 (220 - 222)	32
l	H		3l	15	95	217 - 219 (219 - 222)	12
m	H		3m	25	70	208 - 210 (210 - 212)	25
n	H		3n	25	80	321 - 323 (322 - 324)	25
o	H		3o	20	80	107 (106 - 108)	11
p	H		3p	20	81	67 - 69 (68 - 70)	13
q	Me		3q	15	76	245 - 246 (247 - 248)	24
r	Me		3r	20	70	98 - 99 (98 - 100)	13
s	Me		3s	18	85	173 - 174 (174 - 175)	24
t	Me		3t	20	77	225 - 227 (226 - 228)	21
u	Me		3u	15	83	236 - 238 (238 - 239)	21
v	Me		3v	15	90	275 - 277 (274 - 275)	34
w	Me		3w	20	70	239 (241 - 243)	35
x	Me		3x	20	73	127 (129 - 130)	34

^aAll reactions were carried out with 2 mmol of indole, 1 mmol of aldehyde, 2 ml *Citrus limon* juice, 5 ml water and 3 ml ethanol at pH = 3 at 60°C; ^bYield of the isolated product after chromatography on silica gel.

Table 2. *Citrus limon* juice catalyzed synthesis of tris(indolyl)methanes (5), *p*-bis(indolyl)methyl benzaldehydes (7) and tetra-indoles (8).

Entry	Product	Time (min)	Yield (%)	Melting Point. (°C)		References
				Found	Reported	
a	5a	25	60	246 - 248	249 - 251	35
b	5b	25	75	264 - 267	268 - 269	35
c	7a	25	65	254 - 256	253 - 255	10
d	7b	25	72	230 - 232	232 - 234	35
e	8a	30	68	192 - 194	194 - 195	25
f	8b	30	80	282 - 285	280 - 280	35

bis(indolyl)methane benzaldehydes (7a-b) in good yields. On the other hand, using 4 equivalents of indoles, *p*-di(bis-indolylmethane)benzenes (8a-b) were obtained in high yields within 30 minutes under similar reaction conditions.

All the products are known compounds and their structures are settled by comparison of melting points and spectral (IR, ¹H NMR and Mass) data with their literature data.

3. Conclusion

We have developed an eco-friendly and economic process for the synthesis of bis-, tris-, and tetraindoles by *Citrus limon* juice as a natural catalyst with good yields in aqueous ethanol at pH = 3 at 60°C under ultrasound irradiation. This approach is totally nonpolluting; there is no use of toxic materials, quantifying it is a green approach to this biocondensation reaction between indoles and aldehydes.

4. Experimental Section

4.1. Preparation of Lemon Juice from the Fruits of *Citrus Limon*

Fresh 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.

4.2. General Procedure for Biocondensation of Indoles and Aldehydes by Lemon Juice

Indoles (2 mmol), aldehydes (1 mmol), fruit juice of *Citrus limon* (2 ml), ethanol (3 ml), and water (5 ml) were mixed in a 50 ml round bottomed flask. The reaction mixture (pH = 3) was irradiated in water bath of an ultrasonic cleaner (RIVOTEK with a frequency of 30 kHz and a nominal power 50 W; Riviera Glass Pvt. Ltd.)

at 60°C for the period indicated in **Table 1**. After completion of the reaction, the reaction mixture was diluted with water (5 ml) and extracted three times with ethyl acetate (3 × 10 ml). The combined organic layers were dried over anhydrous sodium sulphate and filtered. And then the solvent from the extract was evaporated under reduced pressure to give the residue, which was purified by column chromatography over silica gel (100 - 200 mesh) using mixtures of petroleum ether and ethyl acetate as eluent to afford the bis(3-indolyl)methanes (3, **Scheme 1, Table 1**) which was finally crystallized from ethyl acetate-petroleum ether. The formation of the products was confirmed by comparison of their physical and spectral data with authentic samples prepared accordingly to previous methods. Tris(3-indolyl)methanes (5) were also synthesized in similar reaction conditions using 2 equivalents of indoles and 1 equivalents of 3-formylindole (4) in 25 minutes (**Scheme 2, Table 2**). Compounds 7 and 8 were also synthesized in similar reaction conditions by choosing the appropriate mole ratios of indoles and aldehydes (**Scheme 3, Table 2**).

4.3. Spectral Data for Representative Compounds

3,3'-Bis(indolyl)-4-methoxyphenylmethane (Compound 3b, **Table 1**): Pinkish solid (yield: 75%), M.p. 183°C - 184°C; IR ν_{\max} (KBr): 3412 and 3401 (N-H), 3050, 2950, 1217, 772 cm^{-1} ; ¹H NMR (CDCl₃, 300 MHz): δ 3.78 (3H, s, OMe), 5.84 (1H, s, Ar-CH), 6.66 (2H, s), 6.81 (2H, d, *J* = 8.17 Hz), 7.00 (2H, t, *J* = 7.5 Hz), 7.16 (2H, t, *J* = 7.5 Hz), 7.24 - 7.40 (6H, m), 7.92 (2H, br s, NH).

3,3'-Bis(indolyl)-4-benzoyloxy-3-methoxyphenylmethane (Compound 3f, **Table 1**): White solid (yield: 85%), M.p. 238°C - 240°C; IR ν_{\max} (KBr): 3399 and 3366 (N-H), 3057, 2966, 1725 (OCOPh), 1276, 743 cm^{-1} ; ¹H NMR (CDCl₃, 300 MHz): 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 (ES⁺): 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 (Compound 3h, **Table 1**): White crystalline solid (yield : 88%), M.p. 216°C; IR ν_{\max} (KBr): 3392 (N-H), 3062, 2950, 1723 (OCOPh), 1270, 745 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 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 (1H, m), 7.95 (2H, br s, NH), 8.19 (2H, d, $J = 9.0$ Hz); HRMS (ES⁺): m/z Calcd for C₃₀H₂₂N₂O₂ [M + Na]⁺ 465.1578, Found 465.1578.

3,3'-Bis(2-methylindolyl)-4-benzoyloxy-3-methoxyphenylmethane (Compound 3v, **Table 1**): White solid (yield: 90%), M.p. 275°C - 277°C; IR ν_{\max} (KBr): 3401 and 3375 (N-H), 3057, 2933, 1725 (OCOPh), 1275, 743; ¹H NMR (DMSO-d₆, 300MHz): 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 (ES⁺): 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 (Compound 3x, **Table 1**): White solid (yield: 73%), M.p. 127°C; IR ν_{\max} (KBr): 3385 (N-H), 3055, 2955, 1458, 1302, 745 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): 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 (ES⁺): 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** (Compound 7b, **Table 2**) Pink solid (yield: 72%). M.p.: 230°C - 232°C. ¹H NMR (300 MHz, 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** (Compound 8b, **Table 2**) Red solid (yield: 80%). M.p.: 282°C - 285°C; IR ν_{\max} (KBr): 3390 (N-H), 3055, 2944, 1454, 1300, 746 cm⁻¹; ¹H NMR (300 MHz, 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.

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