

## Ruthenium<sup>III</sup>-catalyzed condensation of indoles with indole-3-carbaldehyde, a novel synthesis of tris(indolyl)methanes

K. TABATABAEIAN\*, N.O. MAHMOODI, M.GHORANINIA and A. KHORSHIDI

Department of Chemistry, Faculty of Sciences, University of Guilan,  
P. O. Box: 41335-1914 (Iran)

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### ABSTRACT

Synthesis of tris(indolyl)methanes through condensation of various indoles with indole-3-carbaldehyde using Ru<sup>III</sup> as catalyst is reported. It was found that the catalytic system involving Ru<sup>III</sup> affords the products in good to high yields.

**Keywords:** Aldehydes, Tris(Indolyl)methanes, Indoles, Ruthenium.

### INTRODUCTION

The development of new efficient synthetic methods leading to indole derivatives continues to receive much attention in organic synthesis because of their biological activities<sup>1</sup>. Various indole derivatives occur in many pharmacologically and biologically active compounds<sup>2</sup>. Among of them, Bis(Indolyl)methanes possess a wide range of biological activity and their synthesis has received a considerable amount of interest<sup>3,4</sup>. Generally, bis(Indolyl)methanes are prepared by the condensation of indoles with various aldehydes or ketones in the presence of either protic<sup>5</sup> or Lewis acids<sup>6-8</sup>. Zeokarb-225 was also reported as a heterogenous catalyst for the synthesis of bis(indolyl)methanes or tris(indolyl)methanes<sup>9</sup>. On the other hand, Ru<sup>III</sup> salts are well known to catalyze many organic transformations, including aldol and Michael reactions<sup>10</sup>, oxidation reactions of alkanes<sup>11</sup> oxidative cyanation of amines<sup>12</sup>, and many others<sup>13</sup>. In continuation of our recent works on the ruthenium catalyzed reactions<sup>14-16</sup>, here we report the synthesis of Tris(Indolyl)methanes through condensation of various indoles with indole-3-carbaldehyde. It was found that catalytic system

involving Ru<sup>III</sup> affords the products in good to high yields. To the best of our knowledge, this is the first report on the synthesis of Tris(Indolyl)methanes using Ru<sup>III</sup> salts as catalyst.

### RESULTS AND DISCUSSION

Typical results of the Ruthenium catalyzed condensation of indoles with indole-3-carbaldehyde are shown in Table 1, and indicate the scope of the reaction. Treatment of 1-H-Indole-3-carbaldehyde (1 mmol) with indole (2 mmol) in the presence of RuCl<sub>3</sub>.nH<sub>2</sub>O catalyst (1.2 mol %) in methanol (10 mL) at reflux temperature (70°C) for 3 hours, gave corresponding 3,3',3''-tris(Indolyl)methane in 72% isolated yield (product 3a). Compound 3a' was also characterized as a byproduct in 13% yield (Scheme 1) but no other byproducts were observed in the rest of reactions. The reaction can be used for substituted indoles with either electron-donating or electron-withdrawing groups (entries 2-5). Electron-donating substituents however, increased the yield and reaction rate. N-Methylindole and 2-Methylindole were found to be the most reactive substrates and their reactions furnished products 3e and 3b at room temperature in an excellent yield

in 5 and 30 minutes, respectively (Entries 2,5). With regard to regioselectivity, as it is evident from <sup>1</sup>H NMR data, the preferred site for electrophilic substitution was found to be C-3 position of indole. Formation of azafulvenium salt which undergoes further addition with a second indole, rationalized the formation of products from a mechanistic point of view<sup>17</sup>. With the most nucleophilic site (C-3) being blocked, 3-Methylindole underwent condensation from C-2 position as well, and yielded 2-((1H-indol-3-yl)(3-methyl-1H-indol-2-yl)methyl)-3-methyl-1H-indole in good yield. 7-Aza-indole also, reacted well and furnished the desired product.

## EXPERIMENTAL

General. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. <sup>1</sup>H NMR spectra were obtained on a Bruker (DRX-500 Avance). Chemical shifts of <sup>1</sup>H NMR spectra were expressed in parts per million downfield from tetramethylsilane. Melting points were measured on a BÜCHI Melting Point B-540 and are uncorrected. Materials. HPLC grade methanol was used as solvent and all other materials purchased from Merck and used without further purification.

Ruthenium catalyzed condensation of indole and indole-3-carbaldehyde. A 50 mL flask equipped with a magnetic stirring bar was charged with methanol (10 mL), 1-H-Indole-3-carbaldehyde (145 mg, 1 mmol), and indole (234.4 mg, 2 mmol). RuCl<sub>3</sub>.nH<sub>2</sub>O (2.5 mg, 0.012 mmol) was added into the flask and the reaction mixture refluxed at 70°C in an oil bath. After completion of the reaction (3h, checked by TLC), the reaction mixture was purified by preparative TLC (petroleum ether/ethyl acetate: 10/3) providing a pure product (260 mg, 72%).

The same procedure was also used for the other products listed in Table 1.

### 3, 3-(tris-indolyl)-methane. Solid; mp: 216-218 °C

IR (KBr):  $\nu$  (cm<sup>-1</sup>), 426, 463, 490, 602, 750, 798, 1009, 1088, 1217, 1337, 1418, 1454, 2925, 3049, 3405 (br,NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 6.03 (s, 1H), 6.70 (s, 3H), 6.83 (t, J = 7.38Hz, 3H), 7.00 (t, J = 7.35Hz, 3H), 7.269 (d, J = 8.09Hz, 3H), 7.37 (d, J = 7.88Hz, 3H), 9.14 (s, 3H, NH) ppm.

### 3, 3-bis (indolyl)-methane. Solid; mp: 105-107 °C

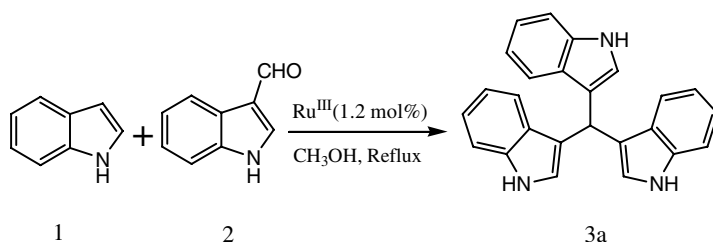
IR (KBr):  $\nu$  (cm<sup>-1</sup>), 430, 455, 509, 570, 609, 770, 794, 1008, 1036, 1090, 1124, 1218, 1290, 1340, 1425, 1454, 2854, 2925, 3060, 3445 (NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 4.30(s, 2H), 7.00(s, 2H), 7.14(t, J=7.40 Hz, 2H), 7.24(t, J=7.63 Hz, 2H), 7.41(d, J=8.11 Hz, 2H), 7.68(d, J=7.8 Hz, 2H), 7.97(br,s,2H,NH) ppm.

### 2, 2-bis (3-methyl indolyl)-3-indolyl-methane. Solid; mp: 93-95 °C

IR (KBr):  $\nu$  (cm<sup>-1</sup>), 430, 460, 490, 580, 745, 1009, 1043, 1095, 1203, 1240, 1265, 1306, 1335, 1458, 2914, 3053, 3402 (NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.32 (s, 6H), 6.24 (s, 1H), 6.79 (d, J = 1.37Hz, 1H), 7.07 (t, J = 3.95Hz, 1H), 7.16-7.21 (m, 5H), 7.26 (t, J = 7.19Hz, 2H), 7.31 (d, J = 9.19Hz, 1H), 7.42 (d, J = 8.18Hz, 1H), 7.64 (t, J = 4.46Hz, 2H), 7.84 (br, s, 2H, NH), 8.14 (br, s, 1H, NH) ppm.




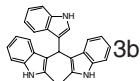

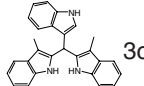
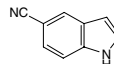
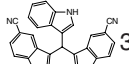

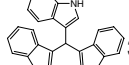

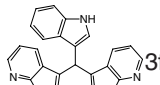
### 3, 3-bis (2-methyl indolyl)-3-indolyl-methane. Solid; mp: 270-272 °C

IR (KBr) :  $\nu$  (cm<sup>-1</sup>), 440, 492, 602, 748, 1009, 1088, 1219, 1298, 1339, 1425, 1460, 2916, 3051, 3450 (NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) :  $\delta$  = 2.39 (s, 6H), 6.19 (s, 1H), 6.82 (s, 1H), 7.07 (t, J = 7.70Hz, 2H),



**Scheme 1: Condensation reaction of indole with indole-3-carbaldehyde and formation of tris(indolyl)methane**

Table 1: Ru<sup>III</sup> catalyzed synthesis of tris(indolyl)methanes

Entry <sup>(a)</sup>	Indole	Aldehyde	Products	Time (min)	Isolated Yield <sup>(b)</sup> (%)
1			3a, 3a'	180	72,13
2		"		30 <sup>(c)</sup>	81
3		"		180	74
4		"		180	68
5		"		5 <sup>(c)</sup>	79
6		"		180	71

<sup>(a)</sup> All products were characterized by <sup>1</sup>H NMR and IR data. <sup>(b)</sup> Isolated yields. <sup>(c)</sup> RT.

7.19 (t, J = 7.59Hz, 4H), 7.42 (d, J = 8.13Hz, 2H), 7.5 (d, J = 9.47Hz, 2H), 7.79 (d, J = 7.83Hz, 2H), 8.01 (br, s, 2H, NH), 8.29 (br, s, 1H, NH) ppm.

**3, 3-bis (5-ciano indolyl) 3-indolyl-methane. Solid; mp: 117-119 °C**

IR (KBr):  $\nu$  (cm<sup>-1</sup>), 430, 491, 638, 775, 808, 1020, 1054, 1097, 1245, 1353, 1429, 1467, 1616, 2219, 2929, 3282, 3426 (NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.71 (s, 1H), 7.32-7.45 (m, 10H), 7.51 (s, 1H), 7.81 (s, 2H), 8.37 (br, s, 2H, NH), 8.48 (br, s, 1H, NH) ppm.

**3, 3-bis (N-methyl indolyl)-3-indolyl-methane. Solid; mp: 215-217 °C**

IR (KBr):  $\nu$  (cm<sup>-1</sup>), 428, 576, 741, 792, 1010,

1124, 1223, 1329, 1463, 2926, 3049, 3409(NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.71 (s, 6H), 5.35 (s, 1H), 6.69 (s, 2H), 6.82 (s, 1H), 7.03-7.07 (m, 3H), 7.19 (d, J = 7.16Hz, 1H), 7.2 (t, J = 7.60Hz, 2H), 7.34 (d, J = 8.20Hz, 2H), 7.4 (d, J = 8.14Hz, 1H), 7.55 (t, J = 7.28Hz, 3H), 7.91 (br, s, 1H, NH) ppm.

**3, 3-bis (7-aza indolyl) 3-indolyl methane. Solid; mp: 268-270 °C**

IR (KBr):  $\nu$  (cm<sup>-1</sup>), 465, 490, 603, 742, 798, 1091, 1217, 1336, 1417, 1454, 1577, 2921, 3060, 3420 (NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.53 (s, 1H), 6.19 (s, 2H), 6.85 (d, J = 1.86Hz, 1H), 6.99 (d, J = 4.76Hz, 2H), 7.06 (t, J = 7.48Hz, 2H), 7.23 (t, J = 7.84Hz, 2H), 7.80 (d, J = 7.83Hz, 2H), 8.29 (d, J = 4.22 Hz, 2H), 9.06 (br, s, 1H, NH), 9.29 (br, s, 2H, NH) ppm.

### CONCLUSION

In brief, we have developed a convenient method for the synthesis of tris(Indolyl)methanes, using condensation reaction of indoles with indole-3-carbaldehyde in the presence of  $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$  as an efficient catalyst in good to high yields. With regard to the previous related works, the advantages of the present protocol are ease of work up, little

waste, shorter reaction times<sup>9</sup> and lower toxicity of the reaction solvent.

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