

## Note

### A convenient one step anodic synthesis of 3-alkyl indoles

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3-Alkyl indoles have been synthesized anodically by co-electrolysis of indole-3-propanoic acid **1** and mono carboxylic acids **2a-2f** viz. propanoic acid **2a**, hexanoic acid **2b**, nonanoic acid **2c**, decanoic acid **2d**, dodecanoic acid **2e** and hexadecanoic acid **2f** at platinum, titanium and graphite. The dimeric products obtained are viz. 1,4 (3'-diindolyl) butane **1'**, alkanes **2'a-2'f** and 3-alkyl indoles **3'a-3'f**. These products have been separated by column chromatography using different solvents and characterized by IR, <sup>1</sup>H NMR and elemental analysis. These studies have suggested that the desired product **3'a-3'f** is obtained in 33-60% yield at platinum anode at current density 0.1111 A.cm<sup>-2</sup>.

Indole-3-substituted compounds are reported to have immense importance e.g. indole-3-acetic acid<sup>1</sup> and indole-3-butyric acid<sup>2</sup> are plant growth hormones. Indole-3-butyric acid enhances enzyme activity in rose<sup>3</sup>, indole-3-butyric acid with CaCl<sub>2</sub> and gibberellic acid increases grain yield in wheat<sup>4</sup> etc. 3-Alkyl indoles are traditionally synthesized from indole magnesium iodide and ethyl iodide in dry ether<sup>5</sup>. 3-Methyl indoles and 3-ethyl indoles have been synthesized by the method described by

Snyder and Smith from acetone and propanal respectively by employing Fischer indole synthesis<sup>6</sup>. Jackson and Smith<sup>7</sup> have also reported the synthesis of 3-sec-octyl indole by the action of indole-3-ethyl magnesium bromide and sec-octyl bromide in 20% yield.

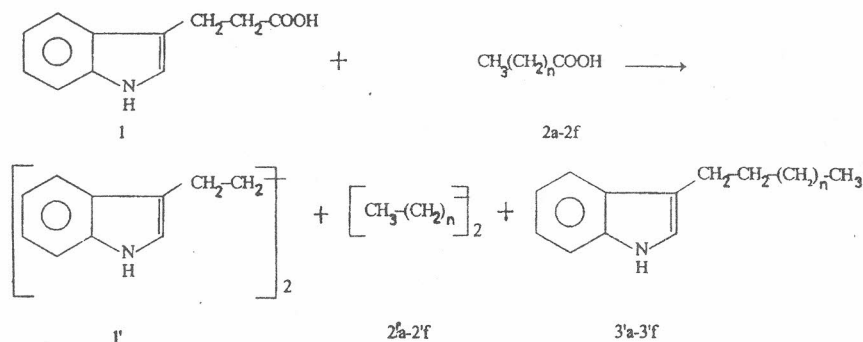
These syntheses involve expensive chemicals and require relatively long methodology and extra care. Recent interest of many research groups in exploiting Kolbe oxidative coupling for synthesis of various class of organic compounds<sup>8</sup> and our interest<sup>9</sup> in this area prompted us to explore the present investigation.

The co-electrolysis of **1** with alkanolic acids **2a-2f** gave **3'a-3'f** along with **1'** and **2'a-2'f**. These products have been characterized by IR, <sup>1</sup>H NMR and elemental analysis. An effort has been made to optimize the reaction pathway.

### Experimental Section

Indole-3-propanoic acid, decanoic acid, dodecanoic acid and hexadecanoic acid were purchased from S.D. Fine Chemicals. Propanoic acid, hexanoic acid and nonanoic acid were purchased from Merck. All chemicals were used without further purification.

Melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Nicolet Megna FT-IR 550 spectrophotometer and <sup>1</sup>H NMR spectra on FX 90 Q JEOL spectrophotometer using TMS as an internal standard.



Where, n = 1,4,7,8,10 and 14

**Cell assembly.** The cell consisted of a 250 ml beaker. The Pt-foil (9cm<sup>2</sup>)/Ti-foil (9cm<sup>2</sup>)/graphite (9cm<sup>2</sup>) were used as anodes. The anode was surrounded by graphite cathodes. No diaphragm was used. The solution was stirred magnetically and a constant current was passed from a current regulated power supply, fabricated by Univ. Science Instrumentation centre, Univ. of Rajasthan, Jaipur. The instrument was calibrated before use.

**Electrolysis.** The electrolysis was carried out as under. The partially neutralized solution **1** and **2a-2f** by sodium methoxide in methanol was anodically oxidized at Pt/Ti/C corresponding to 1F/mole. The temperature was maintained by using ice/cold water. At completion of the reaction the solution becomes alkaline (pH 8.5-10).

**Workup.** After completion of electrolysis, the reaction mixture was filtered. The filtrate was then just neutralized with acetic acid and the solvent was removed by distillation. The residue was diluted with water and extracted with ether (3 × 50 ml). The ethereal layer was extracted with aq. 5% NaOH, which removed the starting material(s) **1** and **2a-2f**. The ethereal layer was dried over anhyd. sodium sulfate and filtered. The ether was distilled to give the mixture of neutral products **1'**, **2'a-2'f** and **3'a-3'f**, which was chromatographed on a silica-gel column and eluted with hexane-ethyl acetate (85 : 15)/benzene-methanol (95 : 5) to give **1'**, **2'a-2'f** and **3'a-3'f**.

Our main goal to undertake this investigation was to develop an efficient, convenient and simpler methodology to synthesize **3'a-3'f** by exploiting Wurtz extension over Kolbe radical coupling. Partially neutralized solutions of compounds **1** and **2a-2f** by calculated quantity of sodium methoxide were oxidized anodically at Pt/Ti/C in methanol by passing charge corresponding to 1F/mole to give products **3'a-3'f** along with **1'** and **2'a-2'f**.

The compounds were separated on a silica-gel column by eluting the products with hexane-ethyl acetate (85 : 15)/benzene-methanol (95 : 5). Products **1'**, **2'a-2'f** and **3'a-3'f** were characterized by spectroscopic methods and elemental analysis. These results are presented in Table I.

The above method seems to be advantageous as reported chemical methods for the synthesis of 3-alkyl indoles involve expensive chemicals, very

specific reaction conditions and consume a lot of time. An effort has been made to optimize the reaction pathway for the anodic cross coupling. These reactions were investigated in detail by varying parameters like degree of partial neutralization, current density, anodic material and molar ratio of **1** and **2a-2f**. These results are discussed systematically.

The reactions have been studied by varying the neutralization of **1** and **2a-2f**.

The data presented in Table II suggest that the maximum yield is obtained when the solution was neutralized to an extent of 50%.

The effect of current passed (current density) was studied by varying the current. These results are grouped in Table III.

Data in Table III suggest that the current of 1.0 amp. is most favourable for the desired product **3'a-3'f**.

The effect of anodic material was studied by performing the reaction at Pt, Ti and graphite. These results are summarized in Table IV.

The lower yield of dimerization at graphite anode is attributed on the basis of the fact that the graphite possess paramagnetic centers within the carbon, which binds the free radical formed and then discharge them as carbonium ion in second electron transfer step<sup>10</sup>.

The molar ratio of **1** and **2a-2f** are varied in order to investigate its effect on the formation of cross coupled products. These data are given in Table V.

The above data indicate that maximum yield is obtained at molar ratio 1:1 except in case of **3'a** where the yield is 8%. This result can be explained in view of the earlier publications<sup>11-13</sup>, wherein, it is mentioned that the short chain carboxylates approach the suitably conditioned anode (oxide layer) in more or less random fashion while to the long chain carboxylates orient perpendicular to the surface of electrode. It is important to mention that the yield of **3'a** was increased by increasing molar ratio of **2a** viz. **1** and **2a** in molar ratio 1:2, 1:6 and 1:10 gave **3'a** in 12%, 38% and 49% respectively. Further increase in molar ratio of **2a** did not increase the yield of **3'a**. The yield of **3'f** is affected severely and it is probably due to the less solubility of **2f** in methanol.

The above results showed that 3-alkyl indoles

Table I—M.P., Elemental Analysis, IR (characteristic bands) and <sup>1</sup>H NMR data of 3-alkyl indoles

Cross product	Mol. formula	m.p. (°C)	Elemental analysis			Characteristic IR (KBr) bands			<sup>1</sup> H NMR, CDCl <sub>3</sub> , (δ ppm) Indole- <sup>b</sup> CH <sub>2</sub> - <sup>a</sup> (CH <sub>2</sub> ) <sub>n</sub> -CH <sub>3</sub>
			C	H	N	-NH stretch	-CH aliphatic stretch	Ring stretch	
3'a	C <sub>12</sub> H <sub>15</sub> N	27	83.41 (83.18)	8.68 8.72	8.03 8.08	3450	2965, 2920, 2850	1600, 1445	0.90 (t, J=5.5 Hz, 3H, -CH <sub>3</sub> ), 1.55-1.67 (m, 4H, -CH <sub>2</sub> (a)), 2.20 (t, J=8 Hz, 2H, -CH <sub>2</sub> (b)), 7.10-7.30 (m, 5H, Indole); 7.35 (s, 1H, -NH).
3'b	C <sub>15</sub> H <sub>21</sub> N	32	83.88 (83.66)	9.80 9.82	6.50 6.50	3450	2950, 2910, 2850	1595, 1470	0.90 (t, J=5.5 Hz, 3H, -CH <sub>3</sub> ), 1.52-1.70 (m, 10H, -CH <sub>2</sub> (a)), 2.28 (J=8 Hz, 2H, -CH <sub>2</sub> (b)), 7.15-7.25 (m, 5H, Indole); 7.40 (s, 1H, -NH).
3'c	C <sub>18</sub> H <sub>27</sub> N	38	84.18 (83.98)	10.53 10.57	5.42 5.44	3445	2955, 2915, 2850	1595, 1465	0.90 (t, J=5.5 Hz, 3H, -CH <sub>3</sub> ), 1.52-1.76 (m, 16H, -CH <sub>2</sub> (a)), 2.34 (t, J=8 Hz, 2H, -CH <sub>2</sub> (b)), 7.10-7.27 (m, 5H, Indole), 7.35 (s, 1H, -NH).
3'd	C <sub>19</sub> H <sub>29</sub> N	40	84.18 (84.07)	10.75 10.76	5.09 5.16	3445	2960, 2920, 2850	1610, 1460	0.90 (t, J=5.5 Hz, 3H, -CH <sub>3</sub> ), 1.50-1.80 (m, 18H, -CH <sub>2</sub> (a)), 2.35 (t, J=8 Hz, 2H, -CH <sub>2</sub> (b)), 7.00-7.29 (m, 5H, Indole), 7.37 (s, 1H, -NH).
3'e	C <sub>21</sub> H <sub>33</sub> N	42	85.62 (84.21)	11.09 11.10	4.61 4.67	3440	2960, 2920, 2850	1600, 1450	0.90 (t, J=5.5 Hz, 3H, -CH <sub>3</sub> ), 1.50-2.10 (m, 22H, -CH <sub>2</sub> (a)); 2.31 (t, J=8 Hz, 2H, -CH <sub>2</sub> (b)), 7.15-7.27 (m, 5H, Indole), 7.38 (s, 1H, -NH).
3'f	C <sub>25</sub> H <sub>41</sub> N	45	87.93 (84.44)	11.56 11.62	3.88 3.93	3440	2960, 2915, 2845	1600, 1465	0.90 (t, J=5.5 Hz, 3H, -CH <sub>3</sub> ), 1.55-2.10 (m, 30H, -CH <sub>2</sub> (a)), 2.30 (t, J=8 Hz, 2H, -CH <sub>2</sub> (b)), 7.00-7.20 (m, 5H, Indole), 7.38 (s, 1H, -NH).

(i) The dimeric compound **1'** has m.p. 126°C, IR : 3450, 2920, 2850, 1600, 1460 etc., <sup>1</sup>H NMR (DMSO) : Indole-<sup>b</sup>CH<sub>2</sub>-<sup>a</sup>(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-Indole : δ 2.8-3.05 (m, 4H, -CH<sub>2</sub>(a)), 3.26 (t, J=9 Hz, 4H, -CH<sub>2</sub>(b)), 7.30-7.58 (m, 5H, Indole); 7.85 (s, 1H, -NH).

(ii) The dimeric alkanes **2'a-2'f** were characterized by IR and <sup>1</sup>H NMR data. These compounds have been found to have m.p./b.p. in agreement to the reported values.

Table II—Anodic oxidation of methanolic solution of **1** and **2a-2f** in molar ratio 1:1 at different neutralizations. Anode Pt, charge transfer 1F/mole, current 1 amp. and current density 0.1111 A. cm<sup>-2</sup>.

Cross product	Neutralization extent%			
	40	45	50	55
	Yield (%) of the cross products			
<b>3'a</b>	28	31	38	28
<b>3'b</b>	47	51	52	44
<b>3'c</b>	37	38	48	37
<b>3'd</b>	40	46	56	45
<b>3'e</b>	41	49	60	46
<b>3'f</b>	21	25	33	29

Table III—Anodic oxidation of 50% neutralized methanolic solution of **1** and **2a-2f** in molar ratio 1:1 at Pt-C at different current densities

Cross product	Current (amp.)		
	0.5	1.0	1.5
	Current density (A. cm <sup>-2</sup> )		
	0.0555	0.1111	0.1666
	Yield (%) of the Cross products		
<b>3'a</b>	16	38	21
<b>3'b</b>	36	52	28
<b>3'c</b>	42	48	42
<b>3'd</b>	23	56	29
<b>3'e</b>	42	60	45
<b>3'f</b>	18	33	29

Table IV—Anodic oxidation of 50% neutralized solution of **1** and **2a-2f** in molar ratio 1:1 at Pt-C, Ti-C and C-C. Current passed 1 amp., current density 0.1111 A. cm<sup>-2</sup>, Charge transfer 1F/mole.

Electrode system	Yield (%) of the cross products					
	<b>3'a</b>	<b>3'b</b>	<b>3'c</b>	<b>3'd</b>	<b>3'e</b>	<b>3'f</b>
Pt-C	38	52	48	56	60	33
Ti-C	28	48	42	50	55	27
C-C	8	20	20	29	31	11

were prepared in good yield by co-electrolysis of **1** and **2a-2f** at current 1 amp., current density 0.1111 A. cm<sup>-2</sup>, molar ratio 1:1, and neutralizing to an extent of 50% at Pt-anode. In case of **1** and **2a**, the molar ratio was 1:10 for the best results, other conditions being the same.

The yields of products **1'**, **2'a-2'f** and **3'a-3'f**, at optimum conditions, described above, are presented in the Table VI.

These data demonstrate that 3-alkyl indoles **3'b-3'f** have been synthesized in the yield 33-60%. It is

Table V—Anodic oxidation of 50% neutralized methanolic solution of **1** and **2a-2f** at Pt. Current passed 1 amp., current density 0.1111 A. cm<sup>-2</sup>, charge transfer 1F/mole

Cross product	Molar ratio of <b>1</b> and <b>2a-2f</b>	
	1:1	1:2
	Yield (%) of the Cross products	
<b>3'a</b>	8	12
<b>3'b</b>	52	45
<b>3'c</b>	48	39
<b>3'd</b>	56	42
<b>3'e</b>	60	48
<b>3'f</b>	33	20

Table VI—Anodic oxidation of 50% neutralized methanolic solution of **1** and **2a-2f**, molar ratio 1:1, electrode Pt-C, current 1 amp., current density 0.1111 A. cm<sup>-2</sup>.

Reactants <b>1</b> and <b>2a-2f</b>	Dimeric product yield (%)		
	<b>1'</b>	<b>2'</b>	<b>3'</b>
<b>2a</b>	25	-	8
<b>2b</b>	17	20	52
<b>2c</b>	15	27	48
<b>2d</b>	14	19	56
<b>2e</b>	16	15	60
<b>2f</b>	26	24	33

- (i) Balance mass in each case was found to be **1** and **2b-2f**.  
 (ii) For entry **2a**, the product **2'a** was not analyzed because the dimer butane is a gas.

to mention that **3'a** was obtained in 49% yield when the reaction was performed in molar ratio 1:10 under above conditions. Further studies for anodic syntheses of other organic derivatives, viz. indole-3-alkanoic acid, indole-3-alkanal and indole-3-alkanol etc., are in progress in this laboratory.

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