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**FIRST ISOLATION OF BOTH INDOLYLCARBINOLS AND DIINDOLYLALKANES FROM MICROWAVE-ASSISTED ACID (CLAY)-CATALYSED REACTION OF INDOLES WITH DIETHYL KETOMALONATE**

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**Abstract-** Indoles (**1a-f**) react with diethyl ketomalonate on montmorillonite K10 clay under microwave irradiation to furnish expeditiously (1-4 min) the corresponding indol-3'-ylcarbinols (**2a-f**; 20-45%) and the respective diindolylalkanes (**3a-f**; 5-35%), which constitute the first direct evidence for the intermediacy of indolylcarbinols in the formation of diindolylalkanes from the acid-catalysed reaction of indoles with aldehydes and ketones.

Diindolylalkanes (DIAs) in general and bis(1*H*-3'-indolyl)alkanes in particular of both synthetic and natural origins are an old<sup>1</sup> and well studied group of compounds, whose synthesis and bioactivity have been recently reviewed.<sup>2</sup> The recent isolation of several DIAs from natural sources<sup>2,3</sup> and their reported significant bioactivities<sup>2,4</sup> render this class of compounds important synthetic targets. As a result, although a wide variety of synthetic routes to the DIAs are available,<sup>2</sup> newer synthetic avenues to these bisindolic compounds continue to be developed.<sup>5</sup> The reaction of indoles with aldehydes or ketones using protic or Lewis acids as catalysts is by far the most widely used route to the DIAs.<sup>6</sup> We have recently demonstrated<sup>7</sup> that montmorillonite K10 clay, possessing both Brønsted and Lewis acidic sites,<sup>8</sup> is also effective for an expedient and efficient synthesis of DIAs by this route. It is well accepted that the DIAs are formed in this type of reactions through the corresponding indolylcarbinols. Although indolylcarbinols along with the corresponding DIAs have previously been reported from the reaction of indolyl Grignard

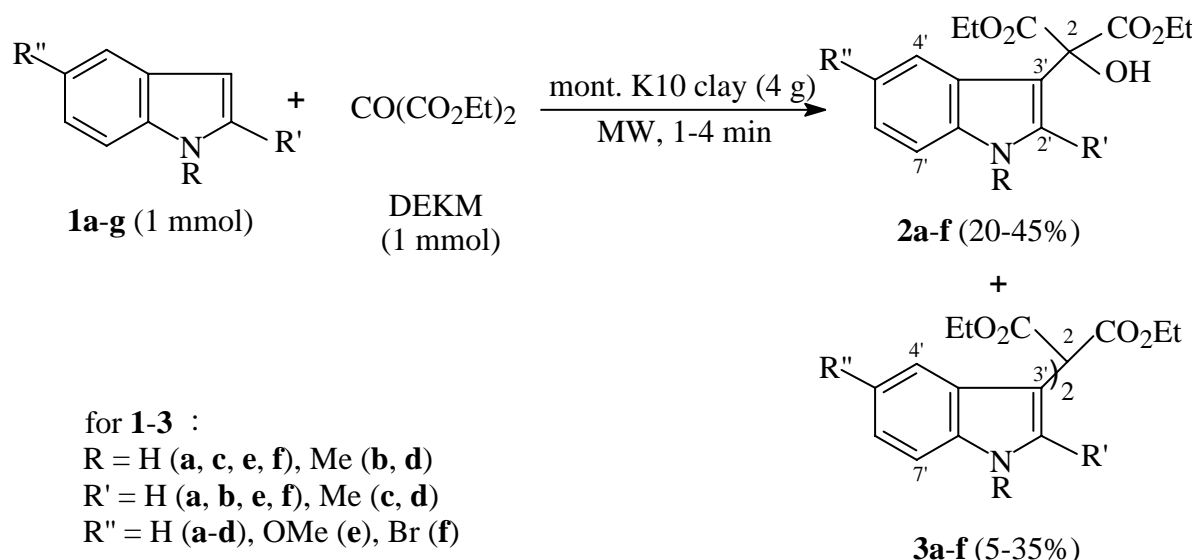
reagents with, for example, pyridine 2- and 4-carboxaldehydes,<sup>9</sup> indolylcarbinols have never been isolated from any acid-catalysed reaction since in the acidic conditions they dehydrate to the corresponding alkylidene indoleninium cations. The latter, though isolated in some cases,<sup>10,11</sup> are usually immediately attacked by a second molecule of the indole, resulting in the formation of DIAs.<sup>12</sup> In continuation of our interest<sup>13</sup> in the clay-mediated reactions of indoles, we recently undertook the study of the microwave-assisted solvent-free<sup>14</sup> reaction of indoles (**1a-f**) with diethyl ketomalonate (DEKM) on K10 clay. As a result, both indolylcarbinols (**2a-f**) and the respective DIAs (**3a-f**) were formed as (except for **1d**) the major and the minor products, respectively, though only in moderate overall yields (28-78%). Our work thus assumes considerable importance from mechanistic viewpoint. We, therefore, present our findings herein.

Initially, indole itself (**1a**) and an equimolar amount of DEKM, adsorbed on the aforesaid clay, was subjected to microwave irradiation,<sup>15</sup> when indole was consumed in a minute to result in the formation of two products (TLC). These were leached from the clay by a suitable solvent, separated into its components by preparative TLC and identified spectroscopically. The major product (20%), analysing for C<sub>15</sub>H<sub>17</sub>NO<sub>5</sub> (also, MS: M<sup>+</sup> 291), recorded in its IR, <sup>1</sup>H and <sup>13</sup>C NMR and MS spectra the presence of a 3-substituted indolyl moiety and two ethoxycarbonyl groups in addition to a hydroxyl group (IR: 3429 cm<sup>-1</sup>; <sup>1</sup>H NMR: δ 4.33, 1H, s) and an oxygenated quaternary (DEPT 135) carbon (δ 78.1). It was thus identified as diethyl 2-hydroxy-2-(3'-indolyl)malonate (**2a**), i.e. an indol-3'-ylcarbinol.

The minor product (8%) also showed the presence of a 3-substituted indolyl moiety and only one ethoxycarbonyl group in its <sup>1</sup>H and <sup>13</sup>C NMR spectra. But from the additional presence of a quaternary carbon (DEPT 135) at δ 58.9 together with its molecular formula, C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> (also, M<sup>+</sup> 390), and the appearance of two (indolic) N-H stretchings (3417, 3362 cm<sup>-1</sup>) in its IR spectrum, it was identified as diethyl 2,2-bis(3'-indolyl)malonate (**3a**), i.e. the DIA generated *via* **2a**. The isolation of **2a** constitutes, to our knowledge, the first isolation of an indolylcarbinol from an acid (clay in this case)-catalysed reaction of an indole with a carbonyl compound.

This significant outcome of our experiment with indole itself prompted us to extend this reaction to a number of substituted indoles in order to check the generality of this observation. Accordingly, each of 1-methyl (**1b**), 2-methyl (**1c**), 1,2-dimethyl (**1d**), 5-methoxy (**1e**) and 5-bromo (**1f**) derivatives of indole was separately but similarly treated with an equimolar amount of DEKM on clay under microwave irradiation until (1-4 min) the reactions were complete. In each case, two products were formed. As in the case of **1a**, both the types of products, **2a-f** (20-45%) and **3a-f** (5-35%), were identified spectroscopically (IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra including DEPT 135, MS, elemental analysis and/or HR MS) as the corresponding

indol-3'-ylcarbinols (**2b-f**) and the DIAs (**3b-f**), respectively (Scheme 1). Pertinently, *N*-methylindole (**1b**) has earlier been reported to react with DEKM in toluene under reflux to furnish **2b** as the sole product. When, however, the same reaction was carried out in presence of the Lewis acid, lithium aluminium dichloride, the corresponding DIA (**3b**) was the only product (38%).<sup>16</sup>



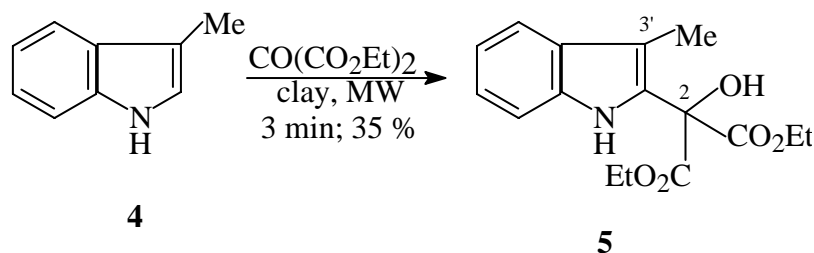
Scheme 1

The two types of products displayed distinguishing spectral behaviour. Thus, in MS spectrum, while each of **3a-f** recorded the base peak at  $M^+ - 73$  m.u. (i.e.  $M^+ - \bullet\text{CO}_2\text{Et}$ ), the same appeared at  $M^+ - 147$  m.u. (i.e.  $M^+ - \text{HCO}_2\text{Et}$ ,  $-\bullet\text{CO}_2\text{Et}$ ) in the case of **2a-f**. In <sup>13</sup>C NMR spectroscopy, C-2 appeared at  $\delta$  78/79 in the case of **2a-f** and at  $\delta$  58 for **3a-f**. In <sup>1</sup>H NMR spectroscopy, although the protons of the two ethoxycarbonyl groups displayed expected splitting patterns in the case of **3a-f** (see EXPERIMENTAL), the two methylene protons of each ethoxycarbonyl group in **2a-f** transpired to be chemical shift non-equivalent, appearing as two signals (2H, dq each,  $J=7, 10.5/11$  Hz) with the six methyl protons appearing as a 6H, dd,  $J_1=J_2=7$  Hz. The individual <sup>1</sup>H and <sup>13</sup>C NMR spectral assignments of one indolylcarbinol (**2c**) were ascertained by analysing its HMQC and HMBC spectra.

Since the acid-catalysed conversion of indolylcarbinols to the corresponding DIAs is well documented,<sup>17</sup> the isolation of the DIAs (**2a-f**) along with the indolylcarbinols (**3a-f**), from which the former are generated, provides the first direct evidence in support of the widely believed intermediacy of indolylcarbinols in the acid-catalysed conversion of indoles to DIAs.

In order to ascertain the influence of electronic factors on the relative yields of the two types of products,

each of skatole (**4**) and 5-nitroindole (**1g**) was separately treated with equimolar amounts of DEKM on clay under microwave irradiation in a similar manner. From **4**, the corresponding indol-2'-ylcarbinol (**5**; 35%) was formed as practically the sole product (Scheme 2) with only traces of the corresponding DIA having been formed. But from **1g**, the corresponding DIA (**3g**; 58%) was practically the sole product, which was quite surprising.



**Scheme 2**

Pertinently, the reactions were also carried out successfully at room temperature or, when necessitated, by heating at 60 °C in an oven. Expectedly, the reactions took longer time for completion, **1g** requiring an appreciably longer period and skatole never going to completion even after exposure to both forms of heating for considerable periods. Clearly, the electron-withdrawing effect of the nitro group in **1g** and the well known reduced nucleophilicity of 3-substituted indoles (**4**) at C-2 are responsible for these observations. The overall findings from our experiments are presented in Table 1.

In order to account for the formation of the indol-3'/2'-ylcarbinols, the first of its kind from such reactions, the fate of the clay-mediated reactions of indoles across the series: acetone<sup>7</sup> to pyruvic acid<sup>18</sup> to DEKM (present work) needed to be considered. In the first two cases, the corresponding DIAs were the sole products. But in the case of DEKM, the DIAs were only either minor products (**3a-c, e, f**) or not formed at all (from **4**), with the indolylcarbinols as the major (**2a-c, e, f**) or the sole (**5**) product(s). The modified carbonyl character of DEKM in comparison to those of acetone and pyruvic acid must be the clue to the contrasting courses of the reactions of these two sets of carbonyl compounds. Since the carbocations are in general electron-deficient,<sup>19</sup> we believe, the destabilizing effect of the two electron-withdrawing carbethoxy groups on the carbocations of type (**6**), through which the DIAs (**3a-f**) are believed to be formed from **2a-f**, largely inhibits the formation of these carbocations in the first place, thereby rendering the formation of the DIAs as only the minor products (except for **3d**). Nevertheless, we are baffled at the formation of **3g** as practically the only product from **1g**.

The intermediacy of the indolylcarbinols in the formation of the DIAs received additional support from

the fact that when the indole (**1c**) was treated with an equimolar amount of the corresponding indolylcarbinol (**2c**) on clay at room temperature, the corresponding DIA (**3c**) was obtained as the only

**Table 1.** Reaction of indoles<sup>a</sup> with DEKM<sup>a</sup> on clay<sup>b</sup> under MW irradiation / at room temperature / 60 °C

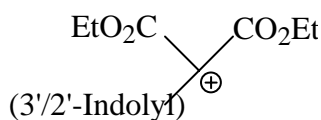
Entry No.	Indoles	R	R'	R''	Time (min)			Products <sup>c</sup> (Yield, %)		Overall yield (%)
					MW	rt	60°C			
1	<b>1a</b>	H	H	H	1	10	—	<b>2a</b> (20)	<b>3a</b> (8)	28
2	<b>1b</b>	Me	H	H	1	10	—	<b>2b</b> (20)	<b>3b</b> (13)	33
3	<b>1c</b>	H	Me	H	1	20	—	<b>2c</b> (35)	<b>3c</b> (31)	66
4	<b>1d</b>	Me	Me	H	1	15	—	<b>2d</b> (30)	<b>3d</b> (35)	65
5	<b>1e</b>	H	H	OMe	1	10	—	<b>2e</b> (23)	<b>3e</b> (5)	28
6	<b>1f</b>	H	H	Br	4	60	15	<b>2f</b> (45)	<b>3f</b> (33)	78
7	<b>4</b>	3-Methyl			3	120	30	<b>5</b> (35) <sup>d</sup>	—	35
8	<b>1g</b>	H	H	NO <sub>2</sub>	18	—	3.5 h	—	<b>3g</b> (58)	58

<sup>a</sup>One mmol of each reactant was used.

<sup>b</sup>For 1 mmol of each reactant, 4 g of montmorillonite K10 clay was used.

<sup>c</sup>Fully identified by IR, <sup>1</sup>H and <sup>13</sup>C NMR, MS spectra and elemental analysis.

<sup>d</sup>The yield of **5** was calculated on the basis of **4** that was consumed.



**6**

product (52%). Notably, the reaction was not complete even after being kept overnight at room temperature, which suggested that the second step in the formation of the DIAs is considerably slower than the first step.

In order to check the recyclability of clay, the clay left after the reaction of **1c** with DEKM was thoroughly washed, dried and then reused in the same reaction in the same scale. The same two products, **2c** and **3c**, were obtained, **2c** in a similar yield (32%) and **3c** in only 12% yield, compared to those using

fresh clay (**2c**: 35%; **3c**: 31%) in the same time period. The recyclability of clay for at least the second cycle in this type of reactions was thus demonstrated, which adds to the usefulness of these reactions.

In conclusion, we have isolated the hitherto elusive indolylcarbinols (along with the corresponding DIAs) from the acid (clay in this case)-catalysed reaction of indoles with carbonyl compounds, diethyl ketomalonate in the present case. The instability of the crucial carbocations (**6**), hence a right choice of the carbonyl compound appears to be the clue to the successful isolation of the indolylcarbinol intermediates.

## EXPERIMENTAL

Mps were determined on a Toshniwal apparatus and are uncorrected. IR (Nujol) spectra were recorded on a Nicolet Impact 410 spectrophotometer, LR EI-MS in AEI MS 30 and JEOL JMS-AX505HA, HR FAB-MS (using *m*-nitrobenzyl alcohol as liquid matrix) in JEOL JMS-700 MStation mass spectrometers and <sup>1</sup>H (500 MHz) and <sup>13</sup>C (125 MHz) NMR spectra, both 1D and 2D, including DEPT 135, in a Bruker DRX 500 NMR spectrometer. Individual <sup>1</sup>H and <sup>13</sup>C NMR assignments of **2c** were based on HMQC and HMBC spectral analyses. TLC was carried out on silica gel G (Merck, India) plates. PE refers to petroleum ether boiling at 60-80 °C. Diethyl ketomalonate was purchased from Lancaster and montmorillonite K10 clay from Fluka.

### Diethyl 2-hydroxy-2-(3'/2'-indolyl)malonates (**2a-f**, **5**) and Diethyl 2,2-bis(3'-indolyl)malonates (**3a-g**). General Procedure

A solution of the indole (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2-3 mL) (except for **1g**) was mixed with a solution (1 mL) of DEKM (from a stock solution of 0.76 mL, 5 mmol in CH<sub>2</sub>Cl<sub>2</sub>, made up to 5 mL) and adsorbed on clay (4 g), and the solvent was allowed to evaporate off at rt. The reactants-on-clay were then subjected in separate lots to MW irradiation (power: 50% for **1a-e**; 70% for **1f**; 80% for **1g** and **4**; each pulse was for 3 min or less) or kept at room temperature or heated in an oven at 60 °C until the indole was consumed (TLC). The clay was then leached with 2% MeOH-EtOAc (3×15 mL), the solvent distilled off from the pooled extracts and the resulting residue separated into its components by preparative TLC in PE-C<sub>6</sub>H<sub>6</sub>-EtOAc (1:2:1). The resulting products were finally purified by crystallisation from PE-CH<sub>2</sub>Cl<sub>2</sub>, unless stated otherwise.

Only for **1g**, 3% MeOH-CH<sub>2</sub>Cl<sub>2</sub> was required to dissolve it, and the products had to be leached with 5% MeOH-EtOAc. In the case of **4**, the reaction did not go to completion even after long exposure to either of the conditions (MW, rt or 60 °C). The reaction was, therefore, terminated at a stage when a maximum amount of the product appeared (TLC; thereafter decomposition started) to be formed. The indole (**4**) was

recovered from this reaction in 34% yield.

**Diethyl 2-hydroxy-2-(3'-indolyl)malonate (2a):** Yield: 58 mg (20%); colourless rods; mp 82 °C; IR: 3429, 3343, 1745, 1712, 751 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.25 (1H, s), 7.71 (1H, d, *J*=8 Hz), 7.37 (1H, d, *J*=2 Hz), 7.28 (1H, d, *J*=8 Hz), 7.16 and 7.10 (1H, t each, *J*=7.5 Hz), 4.34 (1H, s), 4.33 and 4.25 (2H, dq each, *J*<sub>1</sub>=11 Hz, *J*<sub>2</sub>=7 Hz), 1.26 (6H, dd, *J*<sub>1</sub>=*J*<sub>2</sub>=7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 170.6, 136.9, 125.7, 112.4, 78.1 (all C), 124.4, 122.6, 121.2, 120.3, 111.7 (all CH), 63.2 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>); EI-MS: *m/z* (%) 291 (M<sup>+</sup>, 17), 218 (63), 144 (100), 116 (13); Anal. Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>5</sub>: C, 61.86; H, 5.84; N, 4.81. Found: C, 61.66; H, 5.85; N, 4.80.

**Diethyl 2-hydroxy-2-(1'-methyl-3'-indolyl)malonate (2b):** Yield: 61 mg (20%); pale yellow prisms; mp 84-86 °C (lit.,<sup>16</sup> 78 °C); IR: 3468, 1753, 1724, 735 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.70 (1H, d, *J*=8 Hz), 7.36 (1H, s), 7.28 (1H, d, *J*=8 Hz), 7.21 and 7.10 (1H, t each, *J*=7.5 Hz), 4.34 and 4.25 (2H, dq each, *J*<sub>1</sub>=10.5 Hz, *J*<sub>2</sub>=7 Hz), 4.29 (1H, s), 3.75 (3H, s), 1.27 (6H, dd, *J*<sub>1</sub>=*J*<sub>2</sub>=7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 170.6, 137.7, 126.3, 110.7, 78.0 (all C), 128.8, 122.2, 121.4, 120.0, 109.7 (all CH), 63.1 (CH<sub>2</sub>), 33.3, 14.4 (both CH<sub>3</sub>); EI-MS: *m/z* (%) 305 (M<sup>+</sup>, 15), 232 (59), 158 (100), 149 (16), 130 (9); FAB-MS (*m*-NBA): *m/z* 328 (M<sup>+</sup>+Na); Anal. Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub>: C, 62.95; H, 6.23; N, 4.59. Found: C, 62.86; H, 6.25; N, 4.60.

**Diethyl 2-hydroxy-2-(2'-methyl-3'-indolyl)malonate (2c):** Yield: 107 mg (35%); colourless prisms; mp 142 °C (PE-EtOAc); IR: 3443, 3390, 1745, 1725, 754 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.93 (1H, s, NH), 7.36 (1H, d, *J*=8 Hz, H-4'), 7.20 (1H, d, *J*=8 Hz, H-7'), 6.94 (1H, t, *J*=7.5 Hz, H-6'), 6.86 (1H, t, *J*=7.5 Hz, H-5'), 6.58 (1H, s, H-2'), 4.17 and 4.09 (2H, dq each, *J*<sub>1</sub>=11 Hz, *J*<sub>2</sub>=7 Hz, 2×CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.28 (3H, s, 2'-CH<sub>3</sub>), 1.14 (6H, dd, *J*<sub>1</sub>=*J*<sub>2</sub>=7 Hz, 2×CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 171.1 (2×CO<sub>2</sub>Et), 135.4 (C-7'a), 134.4 (C-2'a), 127.8 (C-3'a), 108.5 (C-3'), 79.4 (C-2), 120.8 (CH-6'), 120.5 (CH-4'), 119.2 (CH-5'), 111.2 (CH-7'), 62.0 (2×CH<sub>2</sub>), 14.7 (2×CH<sub>3</sub>), 13.8 (2'-CH<sub>3</sub>); EI-MS: *m/z* (%) 305 (M<sup>+</sup>, 35), 232 (79), 158 (100), 149 (14), 130 (20); FAB-MS (*m*-NBA): *m/z* 328 (M<sup>+</sup>+Na); Anal. Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub>: C, 62.95; H, 6.23; N, 4.59. Found: C, 62.80; H, 6.21; N, 4.61.

**Diethyl 2-hydroxy-2-(1',2'-dimethyl-3'-indolyl)malonate (2d):** Yield: 96 mg (30%); colorless prisms; mp 104-106 °C; IR: 3476, 1737, 1712, 737 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.50 and 7.24 (1H, d each, *J*=8 Hz), 7.13 and 7.04 (1H, t each, *J*=7.5 Hz), 4.38 and 4.25 (2H, dq each, *J*<sub>1</sub>=10.5 Hz, *J*<sub>2</sub>=7 Hz), 4.26 (1H, s), 3.64 and 2.41 (3H, s each), 1.27 (6H, dd, *J*<sub>1</sub>=*J*<sub>2</sub>=7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 171.4, 136.8, 135.9, 126.4, 107.0, 79.0 (all C), 121.2, 120.0, 119.9, 109.2 (all CH), 63.2 (CH<sub>2</sub>), 29.8, 14.3, 12.2 (all CH<sub>3</sub>); EI-MS: *m/z* (%) 319 (M<sup>+</sup>, 42), 249 (95), 172 (100), 40 (45); Anal. Calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>5</sub>: C, 63.95; H, 6.58; N, 4.39.

Found: C, 64.17; H, 6.60; N, 4.38.

**Diethyl 2-hydroxy-2-(5'-methoxy-3'-indolyl)malonate (2e):** Yield: 74 mg (23%); white needles; mp 71 °C; IR: 3423, 3344, 1749, 1730, 1273, 1260, 1215, 1063, 804  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.19 (1H, s), 7.38 (1H, d,  $J=2.5$  Hz), 7.19 (1H, d,  $J=9$  Hz), 7.18 (1H, s), 6.85 (1H, dd,  $J_1=9$  Hz,  $J_2=2.5$  Hz), 4.35 and 4.27 (2H, dq each,  $J_1=10.5$  Hz,  $J_2=7$  Hz), 4.31 (1H, s), 3.83 (3H, s), 1.29 (6H, dd,  $J_1=J_2=7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  170.5, 154.6, 132.0, 126.2, 112.0, 78.1 (all C), 125.0, 113.1, 112.3, 103.0 (all CH), 63.2 ( $\text{CH}_2$ ), 56.2 ( $\text{OCH}_3$ ), 14.4 ( $\text{CH}_3$ ); EI-MS:  $m/z$  (%) 321 ( $\text{M}^+$ , 18), 248 (49), 232 (13), 174 (100); FAB-MS (*m*-NBA):  $m/z$  344 ( $\text{M}^+\text{+Na}$ ); Anal. Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}_6$ : C, 59.81; H, 5.92; N, 4.36. Found: C, 59.89; H, 5.90; N, 4.37.

**Diethyl 2-hydroxy-2-(5'-bromo-3'-indolyl)malonate (2f):** Yield: 166 mg (45%); brown amorphous solid; mp 99-101 °C; IR: 3436, 3317, 1739, 1717, 1021, 807, 792  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.34 (1H, br s), 7.89 (1H, s), 7.37 (1H, d,  $J=2.5$  Hz), 7.24 (1H, dd,  $J_1=8.5$  Hz,  $J_2=2.5$  Hz), 7.14 (1H, d,  $J=8.5$  Hz), 4.344 and 4.27 (2H, dq each,  $J_1=10.5$  Hz,  $J_2=7$  Hz), 4.34 (1H, s), 1.29 (6H, dd,  $J_1=J_2=7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  170.3, 135.5, 127.4, 113.7, 112.1, 78.0 (all C), 125.59, 125.56, 124.1, 113.1 (all CH), 63.4 ( $\text{CH}_2$ ), 14.3 ( $\text{CH}_3$ ); EI-MS:  $m/z$  (%) 371 ( $\text{M}^++2$ , 21), 369 ( $\text{M}^+$ , 21), 298 (70), 296 (70), 224 (100), 222 (100), 196 (7), 194 (7), 143 (20), 115 (10); Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{NO}_5\text{Br}$ : C, 48.65; H, 4.32; N, 3.78. Found: C, 48.54; H, 4.30; N, 3.76.

**Diethyl 2-hydroxy-2-(3'-methyl-2'-indolyl)malonate (5):** Yield: 72 mg (35%); yellow needles; mp 93-95 °C; IR: 3456, 3410, 1739, 738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.92 (1H, s), 7.56 and 7.33 (1H, d each,  $J=8$  Hz), 7.19 and 7.10 (1H, t each,  $J=7.5$  Hz), 4.53 (1H, s), 4.35 and 4.27 (2H, dq each,  $J_1=11$  Hz,  $J_2=7$  Hz), 2.31 (3H, s), 1.29 (6H, dd,  $J_1=J_2=7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  168.7, 133.9, 129.0, 126.5, 110.0, 77.95 (all C), 122.0, 118.7, 118.3, 110.6 (all CH), 62.8 ( $\text{CH}_2$ ), 13.4, 8.8 (both  $\text{CH}_3$ ); EI-MS:  $m/z$  (%) 305 ( $\text{M}^+$ , 37), 232 (73), 158 (100); Anal. Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}_5$ : C, 62.95; H, 6.23; N, 4.59. Found: C, 62.80; H, 6.22; N, 4.61.

**Diethyl 2,2-bis(3'-indolyl)malonate (3a):** Yield: 12 mg (8%); light brown prisms; mp 184-186 °C; IR: 3417, 3362, 1759, 1728, 744  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.04 (2H, s), 7.43 and 7.31 (2H, d each,  $J=8$  Hz), 7.27 (2H, d,  $J=2$  Hz), 7.08 and 6.93 (2H, t each,  $J=7.5$  Hz), 4.22 (4H, q,  $J=7$  Hz), 1.18 (6H, t,  $J=7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  170.4, 136.9, 126.6, 112.9, 58.9 (all C), 125.8, 121.81, 121.80, 119.4, 111.6 (all CH), 61.8 ( $\text{CH}_2$ ), 14.3 ( $\text{CH}_3$ ); EI-MS:  $m/z$  (%) 390 ( $\text{M}^+$ , 21), 317 (100), 289 (9), 243 (13); Anal. Calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 70.77; H, 5.64; N, 7.18. Found: C, 70.60; H, 5.62; N, 7.21.



**Diethyl 2,2-bis(1'-methyl-3'-indolyl)malonate (3b):** Yield: 21 mg (13%); pink needles; mp 145 °C (lit.,<sup>16</sup> mp 172 °C); IR: 1743, 1722, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.47 and 7.27 (2H, d each, *J*=8.5 Hz), 7.21 (2H, s), 7.17 and 6.99 (2H, t each, *J*=7.5 Hz), 4.22 (4H, q, *J*=7 Hz), 3.71 (6H, s), 1.19 (6H, t, *J*=7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 170.5, 137.6, 127.1, 111.7, 58.8 (all C), 130.1, 122.1, 121.7, 119.4, 109.5 (all CH), 62.0 (CH<sub>2</sub>), 33.2, 14.4 (both CH<sub>3</sub>); EI-MS: *m/z* (%) 418 (M<sup>+</sup>, 70), 345 (100), 317 (31), 273 (20), 257 (10), 158 (15), 136 (23); FAB-MS (*m*-NBA): *m/z* 441 (M<sup>+</sup>+Na); Anal. Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.77; H, 6.22; N, 6.70. Found: C, 71.57; H, 6.20; N, 6.68.

**Diethyl 2,2-bis(2'-methyl-3'-indolyl)malonate (3c):** Yield: 42 mg (31%); white needles; mp 228 °C (decomp); IR: 3363, 1718, 1699, 794, 731 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.95 (2H, s), 7.21 and 6.98 (2H, d each, *J*=8 Hz), 6.90 and 6.71 (2H, t each, *J*=7.5 Hz), 3.99 (4H, q, *J*=7 Hz), 2.08 (6H, s), 0.93 (6H, t, *J*=7 Hz); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 169.2, 135.7, 135.6, 128.2, 107.9, 58.7 (all C), 121.2, 120.6, 118.8, 111.1 (all CH), 61.2 (CH<sub>2</sub>), 14.53, 14.50 (both CH<sub>3</sub>); EI-MS: *m/z* (%) 418 (M<sup>+</sup>, 31), 345 (100), 271 (15), 256 (13), 158 (5), 130 (7); FAB-MS (*m*-NBA): *m/z* 441 (M<sup>+</sup>+Na); Anal. Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.77; H, 6.22; N, 6.70. Found: C, 71.90; H, 6.23; N, 6.72.

**Diethyl 2,2-bis(1',2'-dimethyl-3'-indolyl)malonate (3d):** Yield: 54 mg (35%); colorless prisms; mp 214–216 °C; IR: 1732, 750 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>+DMSO-*d*<sub>6</sub>): δ 7.24 and 7.20 (2H, d each, *J*=8.5 Hz), 7.07 and 6.86 (2H, t each, *J*=7.5 Hz), 4.08 (4H, q, *J*=7 Hz), 3.65 and 2.16 (6H, s each), 1.02 (6H, t, *J*=7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>+DMSO-*d*<sub>6</sub>): δ 169.5, 136.8, 136.7, 127.1, 108.2, 58.8 (all C), 121.5, 120.5, 119.0, 108.6 (all CH), 61.2 (CH<sub>2</sub>), 29.8, 14.1, 12.7 (all CH<sub>3</sub>); EI-MS: *m/z* (%) 446 (M<sup>+</sup>, 41), 373 (100), 144 (51), 143 (48); Anal. Calcd for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.64; H, 6.73; N, 6.28. Found: C, 72.44; H, 6.71; N, 6.30.

**Diethyl 2,2-bis(5'-methoxy-3'-indolyl)malonate (3e):** Yield: 9 mg (5%); brown amorphous solid; mp 121 °C; IR: 3385, 1722, 1210, 1029, 801, 724 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.05 (2H, s), 7.26 (2H, d, *J*=2.5 Hz), 7.18 (2H, d, *J*=8.5 Hz), 6.88 (2H, d, *J*=2 Hz), 6.78 (2H, dd, *J*<sub>1</sub>=8.5 Hz, *J*<sub>2</sub>=2.5 Hz), 4.23 (4H, q, *J*=7 Hz), 3.66 (6H, s), 1.21 (6H, t, *J*=7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 170.3, 154.1, 131.9, 127.1, 112.9, 58.8 (all C), 126.2, 112.5, 112.0, 103.7 (all CH), 62.0 (CH<sub>2</sub>), 56.1 (OCH<sub>3</sub>), 14.5 (CH<sub>3</sub>); EI-MS: *m/z* (%) 450 (M<sup>+</sup>, 27), 377 (100), 349 (6), 305 (6), 248 (11), 174 (30); Anal. Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>: C, 66.67; H, 5.78; N, 6.22. Found: C, 66.45; H, 5.80; N, 6.23.

**Diethyl 2,2-bis(5'-bromo-3'-indolyl)malonate (3f):** Yield: 49 mg (33%); brown amorphous solid; mp 82–84 °C; IR: 3383, 1721, 884, 797, 724 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.22 (2H, br s), 7.57 (2H, s), 7.22 (2H, d, *J*=2.5 Hz), 7.20 (2H, dd, *J*<sub>1</sub>=8.5 Hz, *J*<sub>2</sub>=1.5 Hz), 7.15 (2H, d, *J*=8.5 Hz), 4.24 (4H, q, *J*=7 Hz), 1.22 (6H,

t,  $J=7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  170.0, 135.4, 128.1, 113.3, 112.6, 58.7 (all C), 126.8, 125.3, 124.3, 113.1 (all CH), 62.5 ( $\text{CH}_2$ ), 14.3 ( $\text{CH}_3$ ); EI-MS:  $m/z$  (%) 550 ( $\text{M}^++4$ , 34), 548 ( $\text{M}^++2$ , 63), 546 ( $\text{M}^+$ , 33), 477 (94), 475 (100), 473 (95), 449 (14), 447 (28), 445 (15), 355 (29), 353 (29), 282 (61), 280 (61), 236 (16), 224 (26), 214 (17); Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4\text{Br}_2$ : C, 50.36; H, 3.65; N, 5.11. Found: C, 50.20; H, 3.67; N, 5.09.

**Diethyl 2,2-bis(5'-nitro-3'-indolyl)malonate (3g):** Yield: 139 mg (58%); yellow needles; mp 242-244 °C (decomp) ( $\text{C}_6\text{H}_6$ -MeOH); IR: 3429, 3350, 3284, 1732, 1513, 1328, 747  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  11.89 (2H, s), 8.08 (2H, d,  $J=2$  Hz), 7.92 (2H, dd,  $J_1=9$  Hz,  $J_2=2$  Hz), 7.59 (2H, s), 7.55 (2H, d,  $J=9$  Hz), 4.19 (4H, q,  $J=7$  Hz), 1.11 (6H, t,  $J=7$  Hz);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  169.6, 141.2, 140.6, 125.9, 114.4, 58.6 (all C), 130.1, 118.1, 117.4, 113.3 (all CH), 62.8 ( $\text{CH}_2$ ), 14.5 ( $\text{CH}_3$ ); EI-MS:  $m/z$  (%) 480 ( $\text{M}^+$ , 23), 407 (100), 391 (11), 279 (27), 335 (6), 189 (10); Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_8$ : C, 57.58; H, 4.17; N, 11.67. Found: C, 57.71; H, 4.19; N, 11.63.

### Reaction of 1c with 2c on clay

A solution of the indole (**1c**) (131 mg, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was mixed with a solution of the corresponding indolylcarbinol (**2c**) (305 mg, 1 mmol) in EtOAc (3 mL), adsorbed on K10 clay (4 g) and kept at room temperature, but the reaction was not complete even after 2 h. It was, therefore, left overnight at rt. But small amounts of both the reactants were found to be still present. The clay was leached with 2% MeOH-EtOAc (3×15 mL) and the product purified from the remaining **1c** and **2c** by preparative TLC to furnish the corresponding DIA (**3c**) in 52% yield (214 mg), identified by usual comparisons (TLC, co-TLC and mixed mp) with a sample of **3c** obtained from **1c** and DEKM.

### Reaction of 1c with DEKM on recovered clay

The clay left after leaching of the products from the reaction between 1 mmol each of **1c** and DEKM (Entry 3, Table 1) was washed thoroughly with 5% MeOH-EtOAc, dried in a water pump and then heated in an oven at 110°C for 7 h. The indole (**1c**) (131 mg, 1 mmol) was then treated with DEKM (1 mmol, i.e. 1 mL of the stock solution stated earlier) on this recovered clay (4 g) at rt. After **1c** was found to be consumed (20 min), the two products (TLC) formed were leached with 2% MeOH-EtOAc (3×15 mL) and separated by preparative TLC to furnish **2c** and **3c** in 32% and 12% yields, respectively. The products were identified by usual comparisons (TLC, co-TLC and mixed mp) with those obtained from the main experiments.

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