

# Solid Phase Synthesis of Ethyl $\beta$ -Substituted Indolepropionates

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A facile solid phase synthesis of ethyl  $\beta$ -substituted indolepropionates is reported. Condensation between indole, polymer-supported cyclic malonic acid ester and aldehyde yielded the trimolecular adducts, which was cleaved by pyridine/EtOH to release the final products in good yield with high purity.

**Keywords** solid phase synthesis, Meldrum's acid, indole, indolepropionic ester, multicomponent reactions

## Introduction

Synthetic methods for solid phase chemistry have recently undergone a dramatic expansion due to the introduction of combinatorial chemistry into drug discovery.<sup>1</sup> The major reason for this growth is the handling advantages that a solid support provides in the isolation of reaction products, enabling the use of both split-mix and multiple parallel approaches for the synthesis of large compound libraries. Solid phase synthesis is particularly suited to automation because of the ease with which the resin-bound reaction products can be isolated and manipulated.

The diversity generating potential of multicomponent reactions (MCR's) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated. Indolepropionic esters are key intermediates in the synthesis of the antitumor indole alkaloid, ellipticine and its analogues.<sup>3</sup> In solution phase synthesis, the Mannich type condensation of three different carbon components, indole, aldehydes and Meldrum's acid have been explored by Yonemitsu<sup>4</sup> and other groups.<sup>5</sup>

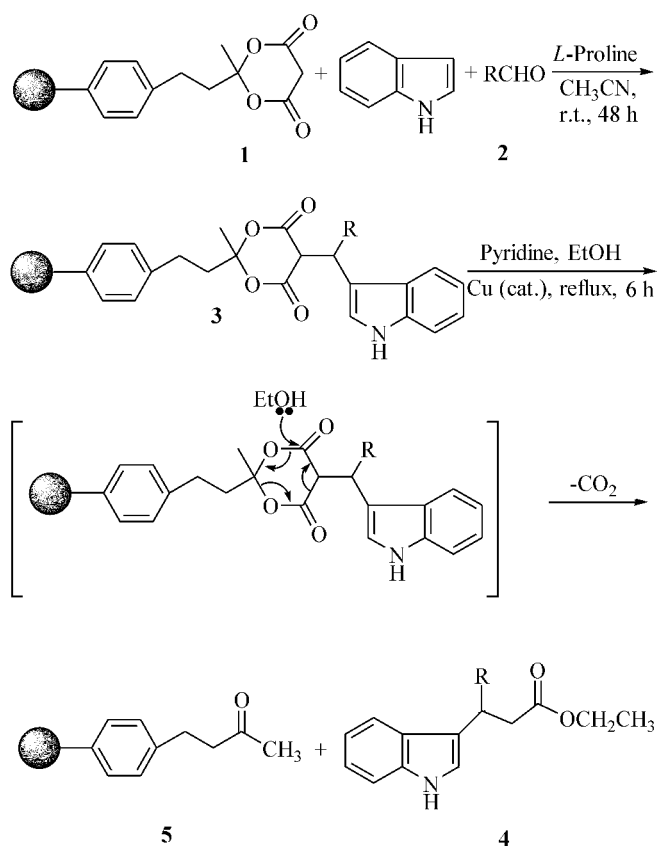
Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) appears to be an attractive reagent in organic synthesis because of its great acidity, steric rigidity and notable tendency to regenerate acetone. It is also a remarkable reagent for synthesis of the heterocyclic compounds.<sup>6</sup> In our previous paper, we have reported the first application of resin-bound Meldrum's acid to solid phase synthesis.<sup>7</sup> To the best of our knowledge, there is no report on the solid phase of indolepropionic esters. In continuation of our work on the resin-bound cyclic malonic acid ester, we try to use this chemistry to the solid phase synthesis of

indolepropionic esters.

## Results and discussion

We reported here an efficient and convenient one-pot synthesis of various ethyl indolepropionates based on the simultaneous condensation of three different carbon components, aldehyde, indole and resin-bound cyclic malonic acid ester, and the subsequent decarboxylative ethanolysis as outlined in Scheme 1.

**Scheme 1**



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Our solid phase synthesis begins with the resin-bound cyclic malonic acid ester **1** which is prepared according to the preliminary communication.<sup>7a</sup> The trimolecular condensation between resin-bound cyclic malonic acid ester **1**, indole and aldehyde **2** was carried out using the proline as catalyst. This conversion was carried out in CH<sub>3</sub>CN at room temperature. After formation of the resin bound condensation products **3**, excess reagents were removed by filtration and washing with the solvents (EtOH, CH<sub>2</sub>Cl<sub>2</sub>). The ethanolysis and decarbonylation of the resin **3** in EtOH/pyridine gave ethyl β-substituted indolepropionates **4** in the presence of copper powder as catalyst.<sup>8</sup> After cleavage, the resin was filtered and washed completely with ethyl ether. The filtrates were washed with dilute hydrochloric acid and dried over MgSO<sub>4</sub>. The products **4** showed good yield and purity (determined by <sup>1</sup>H NMR) after evaporation (Table 1).

**Table 1** Solid phase synthesis of ethyl β-substituted 1*H*-indole-3-propionate

Entry	Product	R	Yield <sup>a</sup> (%)	Purity <sup>c</sup> (%)
1	<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	89	95
2	<b>4b</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	69	85
3	<b>4c</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	84	90
4	<b>4d</b>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	76	95
5	<b>4e</b>	4-ClC <sub>6</sub> H <sub>4</sub>	72	90
6	<b>4f</b>	3-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub>	73	83
7	<b>4g</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	69	90
8	<b>4h</b>	(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	72	85
9 <sup>c</sup>	<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	85	90

<sup>a</sup> The crude yield based on the loading of the resin **1**. <sup>b</sup> Determined by <sup>1</sup>H NMR (400 MHz) spectra. <sup>c</sup> The regenerated resin was used.

For each resin-bound intermediate, the structure was verified by FT-IR spectra. When the resin **1** was transformed to the resin **3**, the carbonyl peak in IR spectra shifted from 1794, 1760 cm<sup>-1</sup> to 1770, 1745 cm<sup>-1</sup> (**3a**, R = Ph). Also a new peak appeared at 3430 cm<sup>-1</sup> (NH group of indole). After cleavage in EtOH/pyridine, the ketone resin **5** was obtained, which showed carbonyl peak at 1716 cm<sup>-1</sup> in IR spectra. The ketone resin **5** can be recovered and reused to prepare the cyclic malonic acid ester resin **1**.<sup>9</sup> The good result was also obtained when the regenerated resin was used (Table 1, Entry 9).

In conclusion, we have studied the proline-catalyzed three-component reaction of aldehyde, indole and polymer bounded Meldrum's acid. This reaction allows the rapid construction of complex and diverse carbon-scaffold with two new C—C σ-bond. The resin-bound condensed products were cleaved under mild condition to provide ethyl β-substituted indolepropionates from polymer-supported cyclic malonic acid ester.

## Experimental

The melting points were uncorrected. <sup>1</sup>H NMR (400

MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in CDCl<sub>3</sub> with TMS as the internal standard; chemical shifts were quoted and *J* values were given in Hz. IR spectra were recorded on a Bruker Vector 22 spectrometer. EIMS was run on an HP 5989B mass spectrometer. DMF (A. R.) and methanol (A. R.) were obtained commercially and used in reactions without any further purification. CH<sub>3</sub>CN and dichloromethane (A. R.) were dried over P<sub>2</sub>O<sub>5</sub> and freshly distilled before use.

### Solid phase synthesis of ethyl β-substituted-1*H*-indole-3-propionate (**4a—4h**)

**General procedure** The mixture of resin **1** (500 mg, loading = 1.20 mmol/g, 1.0 equiv.), indole (0.35 g, 3 mmol, 5.0 equiv.), aldehyde **2** (6 mmol, 10.0 equiv.), *L*-proline (17 mg, 0.15 mmol, 0.25 equiv.) in dry CH<sub>3</sub>CN (5 mL) was stirred for 48 h at room temperature under nitrogen atmosphere. The resin was filtered and washed with 3 × 5 mL of EtOH and with 3 × 5 mL of CH<sub>2</sub>Cl<sub>2</sub> respectively. Then the resin was added to the suspension of EtOH (2 mL), pyridine (20 mL), and active copper powder (20 mg, 0.314 mmol). The mixture was heated to reflux for 6 h. The resin was filtered and washed with ethyl ether in the sintered glass funnel. The filtrate was washed completely with 1 mol/L hydrochloric acid (3 × 5 mL) and H<sub>2</sub>O (10 mL), dried over MgSO<sub>4</sub> and the solvent was evaporated *in vacuo* to afford the product.

#### Ethyl β-Phenyl-1*H*-indole-3-propionate (**4a**)

m.p. 96—98 °C (lit.<sup>4a</sup> 96—98 °C); <sup>1</sup>H NMR δ: 1.07 (t, *J* = 7.1 Hz, 3H), 2.97—3.16 [octet (AB portion of ABX), *J*<sub>AB</sub> = 15 Hz, *J*<sub>AX</sub> = 8.24 Hz, *J*<sub>BX</sub> = 7.6 Hz, 2H], 3.99—4.05 (m, 2H), 4.77—4.80 (t, *J* = 7.88 Hz, 1H), 6.96—6.99 (m, 2H), 7.11—7.17 (m, 2H), 7.21—7.23 (m, 2H), 7.25—7.31 (m, 3H), 7.39—7.41 (1H), 8.05 (1H); IR (KBr) ν: 3351, 2987, 1705, 1618, 1602, 1491, 1458 cm<sup>-1</sup>; MS (70 eV) *m/z* (%): 293 (M<sup>+</sup>, 34), 218 (21), 206 (100), 193 (10), 178 (9), 144 (26), 116 (11), 77 (27).

**Ethyl β-(4-methoxyphenyl)-1*H*-indole-3-propionate (**4b**)** Oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.13 (t, *J* = 7.13 Hz, 3H), 2.93—3.15 [octet (AB portion of ABX), *J*<sub>AB</sub> = 15 Hz, *J*<sub>AX</sub> = 8.45 Hz, *J*<sub>BX</sub> = 7.4 Hz, 2H], 3.74 (s, 3H), 4.01—4.05 (q, *J* = 7.05 Hz, 2H), 4.74 (t, *J* = 7.83 Hz, 1H), 6.78—6.80 (m, 2H), 6.98—7.02 (m, 4H), 7.28—7.41 (m, 2H), 8.05 (s, 1H); <sup>13</sup>C NMR δ: 14.13, 38.528, 41.708, 55.213, 55.604, 60.382, 111.086, 113.805, 114.360, 119.542, 121.077, 122.128, 128.716, 132.025, 135.862, 136.623, 158.122, 172.217; IR (film) ν: 3410, 2933, 1729, 1577, 1370 cm<sup>-1</sup>; MS (70 eV) *m/z* (%): 323 (M<sup>+</sup>, 26), 236 (100), 135 (51). Anal. calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub>: C 74.28, H 6.55, N

4.33; found C 74.62, H 6.19, N 4.42.

*Ethyl β-(4-nitrophenyl)-1H-indole-3-propionate* (**4c**) m. p. 142—144 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.12 (t, J = 7.13 Hz, 3H), 3.00—3.22 [octet (AB portion of ABX), J<sub>AB</sub> = 15.44 Hz, J<sub>AX</sub> = 8.66 Hz, J<sub>BX</sub> = 7.02 Hz, 2H], 4.02—4.14 (m, 2H), 4.88 (t, J = 7.79 Hz, 1H), 6.99—7.03 (m, 1H), 7.07 (s, 1H), 7.14—7.18 (m, 1H), 7.30—7.34 (m, 2H), 7.46—7.48 (d, 2H), 8.09—8.21 (d, J = 8.77 Hz, 2H), 8.24 (s, 1H); <sup>13</sup>C NMR δ: 14.143, 39.135, 40.852, 60.802, 111.397, 117.272, 119.795, 121.319, 122.600, 123.802, 126.219, 128.749, 136.615, 146.682, 151.543, 171.511; IR (KBr) ν: 3411, 2987, 1723, 1518, 1371, 856, 744 cm<sup>-1</sup>; MS (70 eV) m/z (%): 338 (M<sup>+</sup>, 39), 265 (21), 251 (100), 217 (7), 205 (30), 117 (11). Anal. calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 67.44, H 5.36, N 8.28; found C 67.09, H 5.49, N 8.47.

*Ethyl β-(3-nitrophenyl)-1H-indole-3-propionate* (**4d**) m. p. 137—139 °C (lit.<sup>4a</sup> 138—139 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.12 (t, J = 7.07 Hz, 3H), 3.01—3.22 [octet (AB portion of ABX, 2H), J<sub>AB</sub> = 15.35 Hz, J<sub>AX</sub> = 8.6 Hz, J<sub>BX</sub> = 7 Hz], 4.03—4.05 (m, 2H), 4.89 (t, J = 7.83 Hz, 3H), 7.02—7.04 (m, 1H), 7.10 (d, 1H), 7.16—7.18 (m, 1H), 7.33—7.35 (m, 3H), 7.39—7.43 (t, J = 7.93 Hz, 1H), 7.66 (m, 1H), 8.02—8.05 (m, 1H), 8.18 (s, 1H); IR (KBr) ν: 3374, 1727, 1522, 1351, 1180 cm<sup>-1</sup>; MS (70 eV) m/z (%): 338 (M<sup>+</sup>, 33), 321 (39), 265 (15), 251 (100), 217 (10), 205 (31), 115 (6).

*Ethyl β-(4-chlorophenyl)-1H-indole-3-propionate* (**4e**) m. p. 132—134 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.11 (t, J = 7.09 Hz, 3H), 2.97—3.11 [octet (AB portion of ABX), J<sub>AB</sub> = 15 Hz, J<sub>AX</sub> = 8.28 Hz, J<sub>BX</sub> = 7.23 Hz, 2H], 4.01 (q, J = 7.1 Hz, 2H), 4.76 (t, J = 7.83 Hz, 1H), 6.99—7.01 (m, 1H), 7.09—7.15 (m, 1H), 7.29—7.34 (m, 4H), 7.33—7.39 (m, 2H), 8.05 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 13.565, 38.160, 40.773, 60.006, 110.627, 117.813, 118.798, 118.997, 121.792, 125.899, 127.469, 128.017, 128.621, 131.595, 136.044, 141.681, 171.352; IR (KBr) ν: 3374, 1727, 1522, 1351, 1180 cm<sup>-1</sup>; MS (70 eV) m/z (%): 327 (M<sup>+</sup>, 42), 329 (M<sup>+</sup> + 2, 13), 254 (12), 256 (4), 240 (100), 242 (33), 217 (6), 115 (4). Anal. calcd for C<sub>19</sub>H<sub>18</sub>ClNO<sub>2</sub>: C 69.62, H 5.53, N 4.27; found C 69.42, H 5.68, N 4.31.

*Ethyl β-(1,3-benzodioxol-5-yl)-1H-indole-3-propionate* (**4f**) Oil (lit.<sup>4a</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.11 (t, J = 7.2 Hz, 3H), 2.91—3.13 [octet (AB portion of ABX), J<sub>AB</sub> = 15 Hz, J<sub>AX</sub> = 8.40 Hz, J<sub>BX</sub> = 7.6 Hz, 2H], 4.02 (q, J = 7.2 Hz, 2H), 4.71 (t, J = 10 Hz, 1H), 5.88 (s, 2H), 6.68—6.80 (m, 1H), 6.99—7.05 (m, 1H), 7.11—7.17 (m, 1H), 7.31—7.38

(m, 2H), 7.40—7.43 (m, 2H), 8.04 (s, 1H); IR (film) ν: 3374, 1726, 1502, 1486, 1370, 1240, 1180, 1037 cm<sup>-1</sup>; MS (70 eV) m/z (%): 337 (M<sup>+</sup>, 6.6), 278 (2), 250 (19), 213 (10), 196 (3), 91 (100), 65 (24).

*Ethyl β-propyl-1H-indole-3-propionate* (**4g**) Oil (lit.<sup>4a</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.82 (t, J = 7.28 Hz, 3H), 1.11 (t, J = 7.14 Hz, 3H), 1.20 (m, 2H), 1.67—1.75 (m, 2H), 2.69 (d, J = 7.5 Hz, 2H), 3.42 (m, 1H), 3.98—4.04 (q, J = 7.12 Hz, 2H), 6.85 (s, 1H), 6.99—7.01 (m, 2H), 7.16—7.23 (m, 1H), 7.58 (m, 1H), 8.05 (s, 1H); IR (film) ν: 3414, 2957, 1716, 1457, 1173, 1097, 1032, 740 cm<sup>-1</sup>; MS (70 eV) m/z (%): 259 (M<sup>+</sup>, 62), 216 (59), 172 (92), 143 (44), 130 (100), 115 (26).

*Ethyl β-heptyl-1H-indole-3-propionate* (**4h**) Oil (lit.<sup>4a</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.83 (m, 4H), 1.03—1.73 (m, 16H), 2.13—2.33 (m, 2H), 2.69 (m, 2H), 3.42 (m, 1H), 4.00 (q, J = 7.13 Hz, 2H), 6.97 (m, 1H), 7.06—7.14 (m, 2H), 7.15 (m, 1H), 7.29—7.33 (m, 1H), 8.05 (s, 1H); IR (film) ν: 3400, 2926, 2855, 1734, 1458, 1376, 738 cm<sup>-1</sup>; MS (70 eV) m/z (%): 329 (M<sup>+</sup>, 11), 242 (17), 216 (21), 143 (20), 130 (41), 115 (8), 55 (52), 43 (100).

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- 9 The resin was heated in conc. H<sub>2</sub>SO<sub>4</sub> to remove the copper powder and washed with H<sub>2</sub>O , EtOH , CH<sub>2</sub>Cl<sub>2</sub> and dried *in vacuo*. The loading of the regenerated cyclic malonic acid ester is 1.10 mmol/g as determined by reversed titration with hydrochloride acid after saponification with excess NaOH in EtOH.

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