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Meldrum's Acid in Organic Synthesis. V. Versatile One-pot Synthesis of Indolepropionic Esters *via* Simultaneous Condensation of Three Different Carbon Components, Indole, Aldehydes and Meldrum's Acid[1]

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When an acetonitrile solution of Meldrum's acid (**1**), indole (**5**), and an aliphatic or aromatic aldehyde (**8**) in the presence of a small amount of proline (except in the case of acetaldehyde) was allowed to stand at 30°C, a simultaneous condensation of three different carbon components occurred readily to give a 5-(1*H*-indol-3-ylalkyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**11**) in high yield. The reaction proceeded regardless of the nature of the aldehyde. An ethanolysis of **11** with loss of acetone and carbon dioxide took place smoothly in boiling ethanol–pyridine (1: 10) containing a small amount of copper powder to give an ethyl β-alkylindolepropionate (**2**). These two reactions, the condensation and the ethanolysis, were combined in a one-pot procedure, which may provide an efficient and convenient synthetic method for various ethyl indolepropionates (**2**).

Keywords——Meldrum's acid; indole; aldehyde; condensation of three different carbon components; one-pot synthesis; ethanolysis; indolepropionic ester

Until recently, Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**),[2,3] has received little attention, except for its use as a substitute for acyclic malonic esters. However, **1** is now known to be very versatile because of its unusual reactivities due to its great acidity (pK_a 4.97)[4] compared with usual acyclic malonic esters (pK_a 13.7 for ethyl malonate), steric rigidity, and marked tendency to regenerate acetone.

Recently, several reports have described advantages of some derivatives of **1** over their acyclic analogs. Dauben[5] reported an efficient and simple synthesis of δ-damascone based on the use of isopropylidene Meldrum's acid as a dienophile. Trost[6] and Bloch[7] showed that bromo Meldrum's acids are useful as mild brominating agents. Danishefsky[8] synthesized a highly activated cyclopropane derivative of **1**. We reported a general and versatile synthesis of β-keto esters from **1** *via* acyl Meldrum's acids.[9] In the present paper, we report another remarkable example, a versatile and efficient one-pot synthesis of various ethyl indolepropionates (**2**), of the synthetic usefulness of **1**, which is readily accessible from malonic acid and acetone on a relatively large scale.[2]

During the course of our synthetic work on an antitumor indole alkaloid, ellipticine (**3**), and its analogs, the need for an efficient synthetic method for indolepropionic esters (**2**) substituted at the β-position became evident. Indolepropionic acid (**4**) and its esters are readily prepared by the condensation of indole (**5**) and acrylic acid (**6**),[10] but crotonic acid and methacrylic acid gave no condensation products with indole. So far, there is no general and practical method for the synthesis of **2**. Recently, we synthesized ethyl β-methyl-1*H*-indole-3-propionate (**2a**) from a Mannich base (**7**) of indole and ethyl malonate, but the yield was still unsatisfactory.[11]

Since the α-protons of **1** are extraordinarily acidic, it is expected that **1** can react with an electrophile even in the absence of a strong base. Actually, various aldehydes (**8**) react with **1** to give **9**,[3,12] and in some cases a further reaction takes place, namely the Michael addition of a second molecule of **1** as a nucleophile with **9** occurs in the presence[13] and absence[14] of a weak base to give **10**. If another appropriate nucleophile is present in this reaction system, it may react with **9** in place of the second molecule of **1**.

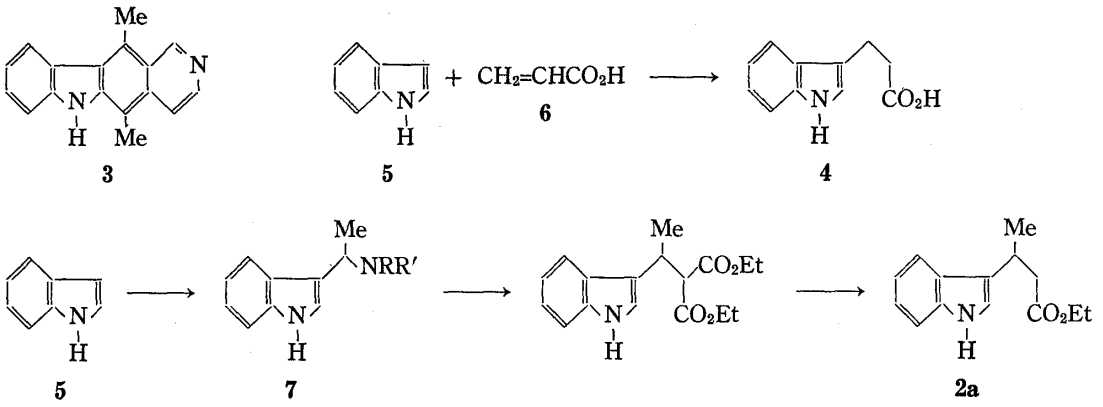


Chart 1

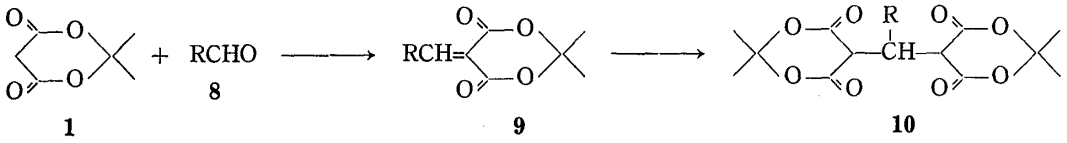
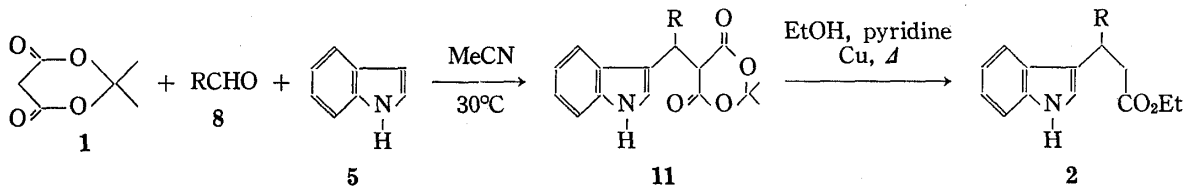


Chart 2

When an acetonitrile solution of a mixture of **1**, acetaldehyde (**8a**), and indole (**5**) (1 : 2 : 1 eq) was allowed to stand at 30°C for 7 h, a new simultaneous condensation of three different carbon components occurred quite smoothly. After evaporation of the solvent, the resulting crystals were washed with hexane to give **11a** in a nearly pure state almost quantitatively.[15] Acyclic malonic esters instead of **1** were completely unreactive under similar conditions. Since this condensation was accelerated by addition of a small amount of proline, various aliphatic aldehydes (**8b**—**h**; 2 eq) with straight and branched chains and aromatic aldehydes (**8i**—**l**; 1 eq) with electron-donating and electron-withdrawing substituents were condensed with **1** and **5** (1 eq each) in the presence of proline (0.05 eq). The reaction proceeded quite smoothly regardless of the nature of the aldehyde to give various condensation products (**11**) in 80—96% yields.[16] The crude products were pure enough for the next reaction, but recrystallization for the solid products (**11a, g**—**l**) and chromatography for the oily products (**11b**—**f**) were employed in order to obtain pure **11**.

The reaction of equimolar amounts of **1** and benzaldehyde (**8i**) is known to give the 2 : 1 product (**10i**) in 93% yield.[14] The addition of **5** (1 eq) as presented here, however, changed the product completely from **10i** to **11i**, clearly indicating that **5** is much more reactive than **1** in the Michael reaction with **9**.



a: R=CH_3
b: R=CH_3CH_2
c: R=$CH_3(CH_2)_2$
d: R=$(CH_3)_2CH$
e: R=$CH_3(CH_2)_3$
f: R=$(CH_3)_2CHCH_2$
g: R=$CH_3(CH_2)_4$
h: R=$CH_3(CH_2)_7$
i: R=C_6H_5
j: R=2,5-$(CH_3O)_2C_6H_3$
k: R=3,4-$(OCH_2O)C_6H_3$
l: R=3-$O_2NC_6H_4$

Chart 3

The direct ethanolysis of **11** to **2** was next examined. Meldrum's acid (**1**) and its monoalkyl derivatives are labile in acidic solution,[17] and when heated with phenols and cyclohexanols, **1** gave malonic acid monoesters in good yields.[18] On the other hand, they are rather stable in alkaline solution because their enolate anions resist the nucleophilic attack of hydroxide anion.[4]

In fact, compounds **11** were almost inert to ethanolysis in the presence and absence of a strong base such as sodium ethoxide, potassium hydroxide, and potassium cyanide, while in the presence of a strong acid such as *p*-toluenesulfonic acid and sulfuric acid **11** disappeared rather rapidly, but gave only a complex product mixture. After several unsuccessful attempts, the most satisfactory results were obtained by ethanolysis in pyridine.

When **11** was heated in ethanol–pyridine (1 : 10), the ethanolysis took place quite smoothly with liberation of acetone followed by gradual decarboxylation to give **2** in a high yield. Addition of a small amount of copper powder accelerated this decarboxylation.

Finally, an efficient and convenient one-pot synthetic method for ethyl indolepropionates (**2**) was established, and a typical example (the synthesis of **2a**) is as follows: an acetonitrile solution of **1**, **8a** and **5** (1 : 2 : 1) was allowed to stand at 30°C for 7 h, and then the solvent was evaporated off *in vacuo* to leave a solid, which, without further purification, was dissolved in ethanol–pyridine (1 : 10) containing a small amount of copper powder and heated under reflux for 3 h. After removal of the solvent and the copper, the residue was distilled under reduced pressure to give ethyl *β*-methyl-1*H*-indole-3-propionate (**2a**) in 80% yield.

Similarly, various ethyl indolepropionates (**2b—g, i—l**) were synthesized in 62—87% overall yields. Purification of undistillable products (**2i—l**) derived from aromatic aldehydes (**8i—l**) was carried out by column chromatography on silica gel.[19]

In summary, the Meldrum's acid procedure presented here may provide an efficient and versatile method for the synthesis of various indolepropionic esters as well as a remarkable example of the novel Mannich-type condensation of three different carbon components.

Experimental

General Procedures for the Preparation of 5-(1*H*-Indol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-diones (11)——a) For **11a**: An MeCN solution (4 ml) of indole (**5**; 234 mg; 2 mmol), acetaldehyde (**8a**: 176 mg; 4 mmol), and 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**: 288 mg; 2 mmol) was allowed to stand at 28—30°C for 7 h. After evaporation of the solvent, the residual colorless crystals were washed with hexane to give almost pure **11a**.

b) For **11b—f**: An MeCN solution (4 ml) of **5** (234 mg; 2 mmol), an aldehyde (**8b—f**: 4 mmol), **1** (288 mg; 2 mmol), and L-proline (12 mg; 0.1 mmol) was stirred at 28—30°C for 24—28 h. After evaporation of the solvent, the residue was passed through a short column of silica gel to give almost pure **11b—f**.

c) For **11g—j**: An MeCN solution (4 ml) of **8g, h** (4 mmol) or **8i, j** (2 mmol), **5** (2 mmol), **1** (2 mmol), and proline (12 mg; 0.1 mmol) was treated as described above. After 18—28 h, the solvent was evaporated off *in vacuo*, and the residue was crystallized by addition of EtOH and collected by filtration to give almost pure **11g—j**.

d) For **11k, l**: **8k, l** (2 mmol) was treated as described above. Colorless crystals precipitated from the reaction mixture were collected by filtration and washed with a small amount of EtOH to give almost pure **11k, l**.

Yields and physical data are as follows.

5-[1-(1*H*-Indol-3-yl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11a**): Yield 98%, mp 119—120°C (dec.) (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1770, 1735. NMR ($CDCl_3$) δ: 1.32 (3H, s), 1.59 (3H, s), 1.65 (3H, d, J=7 Hz), 3.28 (1H, d, J=3 Hz), 4.18—4.52 (1H, m). *Anal.* Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.48; H, 6.13; N, 4.69.

5-[1-(1*H*-Indol-3-yl)propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11b**): Yield 88%, viscous oil. IR ν_{max}^{neat} cm^{-1}: 3400, 1770, 1735. MS *m/e*: 301 (M^+), 199, 170, 158, 149, 84 (base). NMR ($CDCl_3$) δ: 1.62 (3H, s), 3.80 (1H, d, J=3 Hz), 3.92—4.30 (1H, m), 7.1—7.5 (4H, m), 7.6—7.85 (1H, m), 8.2 (1H, s).

5-[1-(1*H*-Indol-3-yl)butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11c**): Yield 93%, viscous oil. IR ν_{max}^{neat} cm^{-1}: 3400, 1770, 1735. MS *m/e*: 315 (M^+), 213, 170 (base), 156. NMR ($CDCl_3$) δ: 0.94 (3H, t, J= 6 Hz), 1.21 (3H, s), 1.61 (3H, s), 3.77 (1H, d, J=3 Hz), 4.02—4.21 (1H, m), 7.0—7.45 (4H, m), 7.6—7.9 (1H, m), 8.5 (1H, s).

5-[1-(1*H*-Indol-3-yl)-2-methylpropyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11d**): Yield 96%, viscous oil. IR ν_{max}^{neat} cm^{-1}: 3400, 1770, 1735. MS *m/e*: 315 (M^+), 213, 170 (base). NMR ($CDCl_3$) δ: 0.84 (3H, d, J=

6 Hz), 1.09 (3H, s), 1.21 (3H, d, J=6 Hz), 1.60 (3H, s), 3.70 (1H, d, J=3 Hz), 3.92 (1H, d, J=3 Hz), 7.05—7.45 (4H, m), 7.6—7.9 (1H, m), 8.25 (1H, s).

5-[1-(1*H*-Indol-3-yl)pentyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11e**): Yield 83%, viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1770 (sh), 1740. NMR ($CDCl_3$) δ: 0.85 (3H, t, J=6 Hz), 1.15 (3H, s), 1.66 (3H, s), 3.79 (1H, d, J=3 Hz), 3.9—4.3 (1H, m), 7.1—7.4 (4H, m), 7.6—7.8 (1H, m), 8.50 (1H, s).

5-[1-(1*H*-Indol-3-yl)-3-methylbutyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11f**): Yield 90%, viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1770 (sh), 1740. NMR ($CDCl_3$) δ: 0.93 (6H, d, J=6 Hz), 1.17 (3H, s), 1.59 (3H, s), 3.75 (1H, d, J=3 Hz), 3.9—4.4 (1H, m), 7.1—7.4 (4H, m), 7.6—7.85 (1H, m), 8.40 (1H, s).

5-[1-(1*H*-Indol-3-yl)hexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11g**): Yield 80%, mp 98—100°C (EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1780, 1740. NMR ($CDCl_3$) δ: 0.85 (3H, t, J=6 Hz), 1.19 (3H, s), 1.60 (3H, s), 3.77 (1H, d, J=3 Hz), 4.00—4.38 (1H, dt, J=3, 9 Hz), 7.1—7.45 (4H, m), 7.6—7.85 (1H, m), 8.30 (1H, s). *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.88. Found: C, 70.04; H, 7.30; N, 4.12.

5-[1-(1*H*-Indol-3-yl)nonyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11h**): Yield 83%, mp 95—99°C (EtOH). *Anal.* Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.71; H, 8.11; N, 3.44.

5-[1*H*-Indol-3-yl(phenyl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11i**): Yield 92%, mp 141—143°C (dec.) (EtOH). *Anal.* Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.02; H, 5.43; N, 4.11.

5-[(2,5-Dimethoxyphenyl)-1*H*-indol-3-ylmethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11j**): Yield 88%, mp 138—139°C (dec.) (EtOH). *Anal.* Calcd for $C_{23}H_{23}NO_6$: C, 67.46; H, 5.66; N, 3.42. Found: C, 67.54; H, 5.70; N, 3.36.

5-[(1,3-Benzodioxol-5-yl)-1*H*-indol-3-ylmethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11k**): Yield 92%, mp 159—162°C (dec.) (EtOH). *Anal.* Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 66.97; H, 4.89; N, 3.40.

5-[1*H*-Indol-3-yl-(3-nitrophenyl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11l**): Yield 87%, mp 174 °C (dec.) (EtOH). *Anal.* Calcd for $C_{21}H_{18}N_2O_6$: C, 63.95; H, 4.60; N, 7.10. Found: C, 63.74; H, 4.54; N, 6.84.

One-pot Synthesis of Ethyl β-Methyl-1*H*-indole-3-propionate (**2a**)——An MeCN solution (120 ml) of **5** (11.7 g; 0.1 mol), **8a** (8.8 g; 0.2 mol), and **1** (14.4 g; 0.1 mol) was allowed to stand at 25—30°C for 4.5—7 h. Removal of the solvent by evaporation *in vacuo* left crystals of **11a**, which were dissolved in pyridine (200 ml). Ethanol (20 ml) and copper powder (2.5 g) were added to the solution, and the mixture was heated under reflux for 3 h. After removal of the solvent *in vacuo*, the residual oil was dissolved in ether and separated from the copper powder by decantation. The ether solution was washed with 2 N HCl and H_2O, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to vacuum distillation to give a colorless oil, **2a** (18.5 g; 80%),[11] bp 179—181°C (2 Torr). IR ν_{max}^{neat} cm^{-1}: 3400, 1720. NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 1.40 (3H, d, J=6 Hz), 2.30—3.05 [2H, octet (AB portion of ABX), J_{AB}=15 Hz, J_{AX}=8 Hz, J_{BX}=6 Hz), 3.35—3.95 (1H, m), 4.10 (2H, q, J=7 Hz), 6.9—7.45 (4H, m), 7.5—7.8 (1H, m), 8.0 (1H, s).

The following ethyl indolepropionates were synthesized in a similar manner.

Ethyl β-Ethyl-1*H*-indole-3-propionate (**2b**): Yield 65%, bp 166—169°C (0.6 Torr). MS *m/e* relative intensity (%): 245 (M^+, 30), 216 (40), 174 (15), 158 (100), 143 (30), 130 (15).

Ethyl β-Propyl-1*H*-indole-3-propionate (**2c**): Yield 62%, bp 160—162°C (0.4 Torr). MS *m/e* relative intensity (%): 259 (M^+, 45), 216 (60), 172 (100), 143 (40), 130 (60).

Ethyl β-(1-Methylethyl)-1*H*-indole-3-propionate (**2d**): Yield 64%, bp 160—164°C (0.3 Torr). MS *m/e* relative intensity (%): 259 (M^+, 25), 216 (100), 174 (25), 172 (30), 143 (40), 130 (15).

Ethyl β-Butyl-1*H*-indole-3-propionate (**2e**): Yield 68%, bp 165—170°C (0.3 Torr). MS *m/e* relative intensity (%): 273 (M^+, 50), 216 (85), 186 (100), 143 (40), 130 (70).

Ethyl β-(2-Methylpropyl)-1*H*-indole-3-propionate (**2f**): Yield 68%, bp 174—177°C (0.3 Torr). MS *m/e* relative intensity (%): 273 (M^+, 50), 216 (65), 186 (75), 143 (45), 130 (100).

Ethyl β-Pentyl-1*H*-indole-3-propionate (**2g**): Yield 63%, bp 182—186°C (0.2 Torr). MS *m/e* relative intensity (%): 287 (M^+, 50), 216 (95), 200 (100), 174 (20), 143 (45), 130 (80).

Ethyl β-Phenyl-1*H*-indole-3-propionate (**2l**): Yield 85%, mp 96—98°C (65% EtOH). *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.69; H, 6.51; N, 4.75.

Ethyl β-(2,5-Dimethoxyphenyl)-1*H*-indole-3-propionate (**2j**): Yield 86%, hard oil. MS *m/e* relative intensity (%): 353 (M^+, 40), 266 (100), 130 (80). The corresponding carboxylic acid, β-(2,5-dimethoxyphenyl)-1*H*-indole-3-propanoic acid, mp 186—187°C (45% EtOH). *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.03; H, 5.91; N, 4.27.

Ethyl β-(1,3-Benzodioxol-5-yl)-1*H*-indole-3-propionate (**2k**): Yield 86%, hard oil. The corresponding carboxylic acid, β-1,3-benzodioxol-5-yl-1*H*-indole-3-propanoic acid, mp 167—168°C (30% EtOH). *Anal.* Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.80; H, 4.84; N, 4.48.

Ethyl β-(3-Nitrophenyl)-1*H*-indole-3-propionate (**2l**): Yield 70%, mp 138—139°C (EtOH). *Anal.* Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.46; H, 5.27; N, 8.23.

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