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MELDRUM'S ACID IN ORGANIC SYNTHESIS. 1. A CONVENIENT ONE-POT SYNTHESIS OF ETHYL INDOLEPROPIONATES

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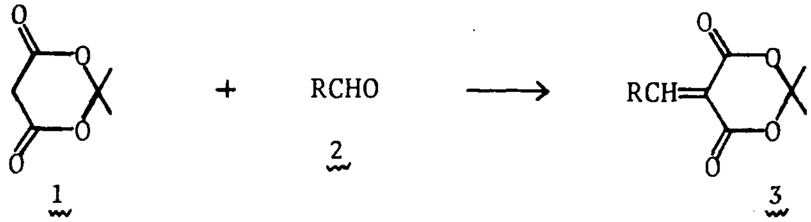
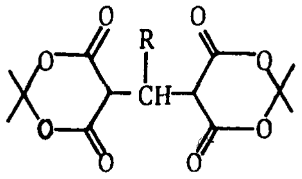
Because of its great acidity (pKa 4.97),[1] steric rigidness, and notable tendency to regenerate acetone, Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione (1),[2] appears to be an attractive reagent in organic synthesis. However, synthetic applications of this acid have received little attention except the use only as an alternative for acyclic malonic esters, whose synthetic utility is well established. Recently, Dauben[3] showed the versatility of an isopropylidene derivative of 1 as a dienophile, because its acyclic analog was unreactive. Trost[4] and Danishefsky[5] also reported useful applications of 1-type compounds, though not derived from 1 itself, showing principal advantages of these compounds over their acyclic analogs. The present investigation was undertaken to develop the synthetic usefulness of 1, readily accessible from malonic acid and acetone in a relatively large scale.

It is expected from the pKa value of 1 that, in contrast with acyclic malonic esters (pKa 13.7),[6] 1 reacts with an electrophile even in the absence of a strong base. Actually, 1 reacts





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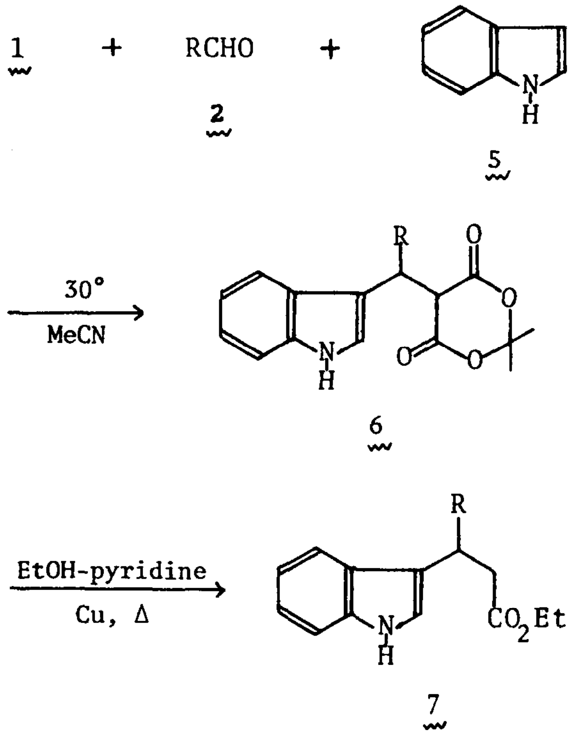
with various aldehydes (**2**) in the presence of a weak base to give **3**.[7] In some cases such as formaldehyde and acetaldehyde, etc., further reaction takes place to give **4**, aldol-Michael products, in the presence[8] and absence[9] of a weak base. If another nucleophile is present in this reaction system, taking the place of the second molecule of **1**, it may react with **3**.

We report here an efficient and convenient one-pot synthesis of various ethyl indolepropionates (**7**)[10] based on the simultaneous condensation of three different carbon components, Meldrum's acid (**1**), aldehyde (**2**), and indole (**5**), and the subsequent decarboxylative ethanolysis as outlined in the following scheme.



a: R = CH_3
b: R = CH_2CH_3
c: R = $(CH_2)_2CH_3$
d: R = $CH(CH_3)_2$
e: R = $(CH_2)_3CH_3$
f: R = $CH_2CH(CH_3)_2$
g: R = $(CH_2)_4CH_3$
h: R = C_6H_5
i: R = $C_6H_4NO_2(3)$
j: R = $C_6H_3(OCH_3)_2(2,5)$
k: R = $C_6H_3(OCH_2O)(3,4)$

When an acetonitrile solution of a mixture of **1**, freshly distilled acetaldehyde (**2a**), and **5** (1:2:1 equiv) was allowed to stand at 30° for 7 hr, a condensation product (**6a**) was isolated almost quantitatively.[14] Since the addition of a small amount of proline accelerated this reaction, various aliphatic (2 equiv) and aromatic (1 equiv) aldehydes other than **2a** were condensed with **1** and **5** (1 equiv each) in the presence of 0.05 equiv of proline. The condensation proceeded quite smoothly, regardless of the aldehyde, and the results are summarized in Table I.

The reaction of **1** and benzaldehyde (**2h**) in a 1:1 molar ratio is known to give **4h** in 93% yield.[9] The addition of 1 equiv of **5** as presented here, however, changed the product completely to **6h**, indicating that **5** was much more reactive than **1** in the Michael reaction with **3**.

The direct conversion of 6 to 7 was next examined. Meldrum's acid (1) and its monoalkyl derivatives are labile in acid solution[15] but rather stable in alkaline solution because their enolate anions resist the nucleophilic attack of hydroxide ion.[1] In fact, 6 was almost inert to ethanolysis in the presence and absence of a strong base such as potassium hydroxide, sodium ethoxide, and potassium cyanide. Unfortunately, treatment of 6 with toluenesulfonic acid (or sulfuric acid) in ethanol gave complex products. When 6 was heated in ethanol-pyridine, however, smooth ethanolysis took place with concomitant decarboxylation, which was accelerated by the addition of a small amount of Cu-powder.

Finally, a convenient one-pot synthetic method of ethyl indolepropionates (7) was established as follows: After the mixture of 1, 2a, and 5 was condensed as described above, the acetonitrile was evaporated in vacuo. The residue (6a) without further purification was dissolved in ethanol-pyridine (1:10) containing a small amount of Cu-powder and heated under reflux for 3 hr. After removal of the solvent and Cu-powder, the vacuum distillation of the residue gave 7a in 80% yield. Similarly various ethyl indolepropionates (7b-7k) were synthesized as summarized in Table II.[16]

In summary, the results presented here may provide an efficient and convenient method for the preparation of various indolepropionic esters as well as an example of the novel Mannich-type condensation of three different carbon components.

Table I. Condensation Products (6) of 1, 2, and 5 at 30°.

Product	Reaction Time,hr	Yield,%	mp° C
6a	7	98	119-122(dec)
6b	10	88	(oil)
6c	10	93	(oil)
6d	10	96	(oil)
6e	10	83	(oil)
6f	10	90	(oil)
6g	10	80	98-100
6h	18	92	141-143(dec)
6i	22	87	174(dec)
6j	24	88	138-139(dec)
6k	30	92	159-162(dec)

Table II. Yields of Ethyl Indolepropionates (7).

	Yield,%[a]	bp°C/Torr(mp°C)
7a	80	179-181/2
7b	65	166-169/0.6
7c	62	160-162/0.4
7d	64	160-164/0.3
7e	68	165-170/0.3
7f	68	174-177/0.3
7g	63	182-186/0.2
7h	87	(96-98)
7i	70	(138-139)
7j	68	oil(186-187)[b]
7k	68	oil(167-168)[b]

[a] See footnote 17. [b] footnote 18.

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(10) Ethyl indolepropionates (**7**) are required as starting materials for the synthesis of antitumor elipticine analogs.[11] However, there is no practical method of obtaining indolepropionic acids and their esters. Indolepropionic acid itself can be synthesized from indole and acrylic acid,[12] but substituted acrylic acids such as crotonic acid do not react with indole. Recently, **7a** was synthesized from N-(3-indolyl-1-ethyl)-N-isopropylamine and diethyl malonate only in 27% yield.[13]

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(14) This reaction can be explained as an extension of the Mannich reaction in terms of a condensation of three different components. The use of **1** (carbanion) instead of amines (hetero atom) leads to a facile condensation of three different carbon components. Under similar conditions, dimethyl malonate was completely unreactive.

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(16) Purification of **7h**-**7k** derived from aromatic aldehydes (**2h**-**2k**) was carried out by column chromatography because **7h**-**7k** could not be distilled. When condensation products (**6h**-**6k**), which separated out from the reaction solution (in case of **6i** and **6k**) or crystallized by the addition of ethanol to the evaporated residue (in case of **6h** and **6j**), were collected by filtration and then subjected to the decarboxylative ethanolysis, almost pure **7h**-**7k** were isolated without chromatographic purification.

(17) Yields of **7a**-**7g** are based on **5** by one-pot reactions. Yields of **7h**-**7k** are based on isolated **6h**-**6k**.

(18) Mp of the corresponding carboxylic acids.