there is a higher positive charge on the β carbon.[9] These data suggest that the reactions with nucleosides should also begin at the β carbon. An alternative mechanism would have initial attack by water, with the nucleoside attacking the intermediate quinone imide methide. Further pursuit of this mechanism, however, leads to structures which appear less likely than those proposed in Scheme I.

It is clear that the mechanism shown in Scheme I, or one of the alternatives suggested above, could apply equally well to any reaction which would result in an initial adduct bearing a hydroxyl group vicinal to N-3. Such a reaction could well take place between cytidine or a nucleic acid and a hydrocarbon epoxide. Reaction of benzo[*a*]pyrene-7,8-dihydrodiol 9,10-oxide with poly(C) in vitro[10] and with cytosine in RNA in tissue explants[11] has already been demonstrated. However, it has not been established that the products are actually cytosine compounds. In light of our finding, it appears worthwhile to undertake structural studies on the putative benzpyrene–cytidine adducts.

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Meldrum's Acid in Organic Synthesis. 2. A General and Versatile Synthesis of β-Keto Esters

Summary: On acylation with various acyl chlorides Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, gave the corresponding acyl Meldrum's acids, which readily underwent alcholysis with methanol, ethanol, *tert*-butyl alcohol, benzyl alcohol, and trichloroethanol to give various β-keto esters; the acyl Meldrum's acids can be regarded as a synthetic equivalent of mixed diketenes.

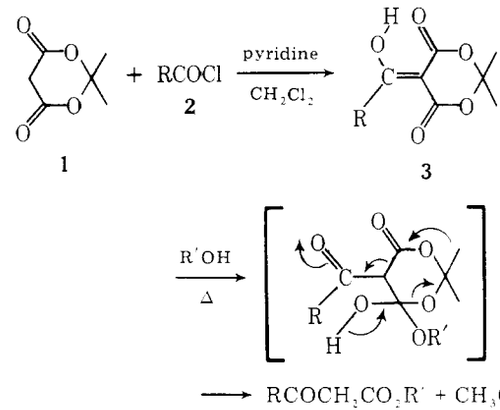
Sir: Since the first example of the Claisen condensation was discovered more than a century ago, β-keto esters have been one of the most important intermediates in organic synthesis.[1] However, it is still required to establish a general and practical method for the preparation of arbitrary β-keto esters of the type $RCOCH_2CO_2R'$.[2] Among the many methods for synthesizing β-keto esters of the type $RCOCH_2CO_2C_2H_5$, two classical syntheses via acetoacetic esters[4] and via mixed malonic esters[5] rather than some modern methods[6] are practically useful, though not always satisfactory in yield, and none is capable of modifying the ester group. We wish to report here a general and versatile method for the synthesis of β-keto esters based on the noteworthy reactivity of Meldrum's acid (**1**), 2,2-dimethyl-1,3-dioxane-4,6-dione,[7] as outlined in Scheme I.

Table I. Yields of Various β-Keto Esters (4–7)[a]

Starting chloride	Yield, % 4	5	6	7
2a	82	74	74	86
2b	79	70	77	75
2c	75	74	80	78
2d	84	80	80	82
2e	86	78	71	75
2f	90	77	73	74
2g	92	85	79	80
2h	85	82	60	74
2i	79	84	74	82
2j	81	78	78	73
2k	69	73	73	71

[a] See footnote 19.

Scheme I



4, R′ = CH_3
5, R′ = CH_2CH_3
6, R′ = $CH_2C_6H_5$
7, R′ = $C(CH_3)_3$

a, R = CH_2CH_3
b, R = $(CH_2)_2CH_3$
c, R = $(CH_2)_3CH_3$
d, R = $(CH_2)_4CH_3$
e, R = $(CH_2)_5CH_3$
f, R = $(CH_2)_6CH_3$
g, R = $(CH_2)_7CH_3$
h, R = $(CH_2)_7CH{=}CH_2$
i, R = $CH_2C_6H_5$
j, R = $(CH_2)_2CO_2CH_3$
k, R = $(CH_2)_2OCH_2CH_3$

In marked contrast with acetoacetic esters (pK_a 10.7)[8] and acyclic malonic esters (pK_a 13.7),[8] **1** readily reacts with electrophiles such as aldehydes even in the absence of a strong base[9] because of its great acidity (pK_a 4.97).[10] Therefore, acylation of **1** is also expected to occur under similar conditions. When a dichloromethane solution of **1** was treated with 1.1 equiv of propionyl chloride (**2a**) in the presence of pyridine (2 equiv) at 0 °C for 1 h and then at room temperature for 1 h under nitrogen, an acyl Meldrum's acid (**3a**) [mp 55 °C; δ (CCl_4) 1.26 (3 H, t, J = 7 Hz), 1.70 (6 H, s), 3.08 (2 H, q, J = 7 Hz), 15.0 (1 H, s)] was isolated in almost quantitative yield.[11] Similarly, **1** was acylated with various chlorides (**2b–k**) to give the corresponding acyl Meldrum's acids (**3b–k**) almost quantitatively.[12]

Although ethanolysis of **1** and its monoalkyl derivatives

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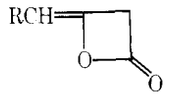
proceeds quite slowly without acid catalyst,[9] its acyl derivatives (3) are expected to undergo easily the ethanolysis because of enolization of the acyl group.[11] When the crude **3a**[13] was heated in methanol under reflux, the methanolysis took place smoothly with the evolution of carbon dioxide. After 2 h, the solvent was evaporated and the residue was distilled under reduced pressure to give methyl propionylacetate (**4a**)[5a] in 82% yield from **1**. Various methyl acylacetates (**4b–k**) were similarly synthesized. In the same manner, the ethanolysis of **3** also proceeded readily to give the corresponding ethyl esters (**5a–k**) in good yield. The results are summarized in Table I.

The reactivity of **3** in alcoholysis is comparable to that of diketene,[14] which is known to be susceptible to attack by various nucleophiles such as alcohols[15] and amines[16] to give acetoacetic acid derivatives. Therefore, **3** can be regarded as a synthetic equivalent of mixed diketene **8**, which is usually not available.



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This alcoholysis of **3** was extended to the synthesis of acylacetic acid benzyl and *tert*-butyl esters without any difficulty. A benzene solution of **3** containing 3 equiv of benzyl alcohol or *tert*-butyl alcohol was refluxed for 3 h. After evaporation of the solvent, the residue was distilled to give **6** or **7** in good yield. The results are also summarized in Table I.

Finally, some trichloroethyl esters,[17] which can be hydrolyzed by zinc in acetic acid,[18] were synthesized in fair yield.[19]

$$RCOCH_2CO_2CH_2CCl_3$$

9a, R = $CH(CH_3)_2$; 67%

b, R = $(CH_2)_2CO_2CH_3$; 70%

c, R = $(CH_2)_2OCH_2CH_3$; 67%

Further applications of this simple and versatile synthesis of β-keto esters to some developments of the Carroll reaction,[20] indole synthesis,[21] etc., are currently in progress.

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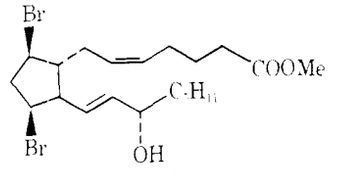
Prostaglandin H_2 Methyl Ester

Summary: Prostaglandin H_2 methyl ester has been prepared in 20–25% yield from 9β,11β-dibromo-9,11-dideoxyprostaglandin $F_{2\alpha}$ with silver trifluoroacetate and hydrogen peroxide.

Sir: The prostaglandin endoperoxides PGH_2 and PGG_2 have attracted considerable attention in recent years. These intermediates in prostaglandin biosynthesis play an important role in diverse physiological functions such as blood platelet aggregation,[1-3] and an understanding of the chemistry and pharmacology of these species may well provide new insights into the chemical mechanism of heart attack and stroke.[4] Several different synthetic approaches to the 2,3-dioxabicyclo[2.2.1]heptane system have been reported[5,6] and recently the Upjohn group of Johnson, Nidy, Baczynskyj, and Gorman[7] have reported a synthesis of PGH_2 methyl ester (**2**) in 3% yield from 9β,11β-dibromo-9,11-dideoxyprostaglandin $F_{2\alpha}$ methyl ester (**1**). The method reported by Johnson et al.[7] involves reaction of **1** with potassium superoxide[8,9,10] in an S_N2 displacement reaction. Inasmuch as the yields of **2** formed by the



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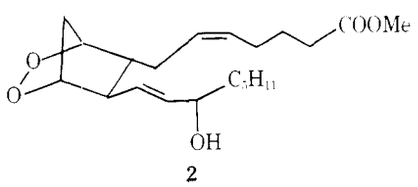

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superoxide method are low, and prospects for yield improvement are limited,[7] we have sought to develop other methods for carrying out the conversion **1** → **2**. In particular, the potential conversion of **1** to **2** by silver salts and hydrogen

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