COMMUNICATIONS

- New or improved synthetic methods
- Key intermediates
- with full experimental and analytical data

A Modified Preparation of β-Keto Esters

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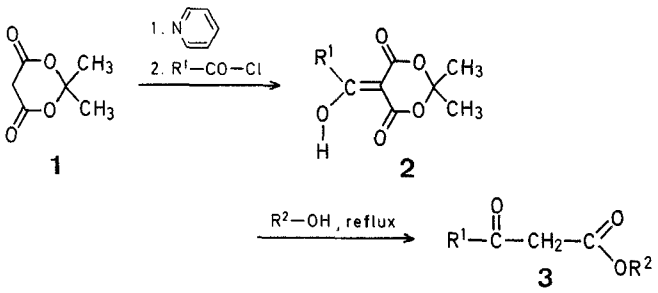
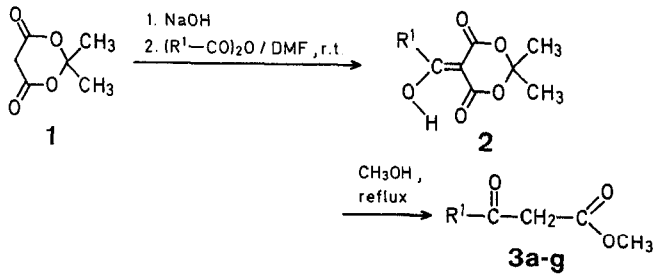
Many methods[1] have been developed for the preparation of β-keto esters, versatile intermediates in organic synthesis. A high proportion of these methods involve the initial conversion of a malonic acid derivative into the mono- or di-anion by the action of a base such as a metal alkoxide, an organo-lithium reagent, or a tertiary amine, followed by acylation with a carboxylic acid derivative. Both these steps are involved in one of the most general methods currently available for preparing β-keto esters, i.e. that described by Yonemitsu and coworkers[2] in 1978. In this method, Meldrum's acid **(1)** is treated with pyridine in order to generate the mono-anion, and this is then acylated with a carboxylic acid chloride (R^1—CO—Cl) to give the *C*-acylated derivative which usually exists largely in the enol form **2.** When heated under reflux with an alcohol (R^2—OH), the acyl derivative is rapidly converted into the β-keto ester **3.**



Although this method is very versatile, it does have limitations. For example, in all the β-keto esters whose preparation was reported by Yonemitsu and coworkers, the group R^1 is bonded to the keto group through an sp^3-hybridised carbon. We have found that when R^1 is 4-O_2N—C_6H_4, only very poor yields of the β-keto ester **3f** are obtained. Furthermore, this method utilises an acid chloride as the acylating agent, and currently there are very few methods[3] available for preparing this type of compound when the acyl group contains an acid-sensitive substituent. Also the anion of Meldrum's acid is generated under basic conditions, and therefore the method is unsuitable for preparing β-keto esters of type **3** in which the group R^1 contains a base-sensitive substituent. In this communication, we report the preparation of some β-keto esters **3** by a modification of the above method which appears to overcome these limitations.



The sodium salt of Meldrum's acid, which is conveniently obtained by the action of aqueous sodium hydroxide on the acid, was first reported by Meldrum[4] in 1908 and, in the absence of moisture, is a stable crystalline solid. We have found that in dimethylformamide the salt is readily acylated by carboxylic anhydrides at room temperature to give acyl derivatives with structure **2** which are conveniently converted into methyl keto esters **3** (R^2=CH_3) by heating in methanol under reflux for 2 h. For example, with the anhydride of phenylacetic acid the sodium salt gave **2** (R^1=C_6H_5—CH_2) which on methanolysis gave the β-keto ester **3a** in 83% yield based on the anhydride. At all stages, the preparation of the β-keto ester involved mild conditions which were neither strongly acidic nor basic, for the anion of Meldrum's acid was used in the form of a sodium salt which, in solution, is only weakly basic on account of the relatively high acidity of the parent acid (pK_a 4.97 in water)[5], while the anhydride was prepared from the parent carboxylic acid by the action of dicyclohexylcarbodiimide[6]. This diimide is, of course, one of the many reagents which effect the formation of anhydrides from carboxylic acids under mild and non-acidic conditions[7].

Other β-keto esters **3b-g,** all but one of which contain functional groups in the acyl or aroyl residue, were prepared by the same method, and although no attempts were made to maximise the yields in most cases these were comparable with those reported in the literature for alternative preparations (see Table). The one exception to this was provided by compound **3d** whose yield was very low on account of the rapidity with which the anhydride of *N*-(benzyloxycarbonyl)-glycine used as the acylating agent rearranges in solution at room temperature[8,9]. In all cases, the ^{1}H-N.M.R. spectral data of the keto esters (in deuteriochloroform) were in agreement with literature values, the characteristic features being a singlet at δ=3.6 ppm (3H, $COOCH_3$) and a singlet (CO—$C\underline{H}_2$—CO) which occurred in the range δ=3.46 (for **3b**) to 4.0 ppm (for **3f**). The relative intensity of the latter signal showed that with the exception of the two aroylacetates (**3e** and **f**) the keto esters existed very largely in the keto form in deuteriochloroform. The spectrum (δ=4.25, C=C$\underline{H}$) of **3f** indicated the very high degree of enolisation noted by other workers[10,11] for the corresponding ethyl ester.

Sodium Salt of Meldrum's Acid:

Meldrum's acid[12] (**1**; 11.5 g, 80 mmol) is added to a stirred solution of sodium hydroxide (2.78 g, 70 mmol) in water (50 ml) at 10 °C, and then the excess of acid is removed by filtration. The water is removed from the filtrate under reduced pressure keeping the temperature below 50 °C, and the residual solid is dried under vacuum to leave the colourless sodium salt of **1**; yield: 11.1 g (96%).

^{1}H-N.M.R. (DMSO-d_6): δ=8.50 ppm (s, 6H).

β-Keto Esters 3a-g; General Procedure:

The carboxylic anhydride (30 mmol) in dry dimethylformamide (20 ml) is added dropwise during 5 min to a stirred suspension of the sodium salt of Meldrum's acid (30 mmol) in dry dimethylformamide (50 ml) at 0 °C under nitrogen, the mixture is stirred at 0 °C for 1 h, and then at 20–30 °C for 18 h. Dichloromethane (100 ml) followed by 2

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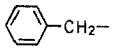
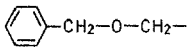
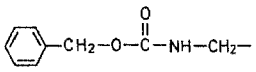
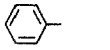
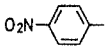
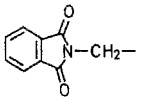
Table. β-Keto Esters **3a-g** ($R^2 = CH_3$)

Product No.	R	Yield [%] found[a]	Yield [%] reported	m.p. [°C] or b.p. [°C]/torr found	m.p. [°C] or b.p. [°C]/torr reported	^{1}H-N.M.R. ($CDCl_3$, 100 MHz)[b] $\delta_{CH_2-CO-CH_2-CO-}$ [ppm] found	^{1}H-N.M.R. ($CDCl_3$, 100 MHz)[b] $\delta_{CH_2-CO-CH_2-CO-}$ [ppm] reported
3a		83	65-70[13]	118-119°/1	125°/3[13]	3.74 (s)	3.78 (for $R^2 = C_2H_5$)[1]
3b	$C_2H_5-O-CH_2-CH_2-$	42	25[14]; 27[15]	80°/0.8	90-94°/3[15]	2.75 (t)	—
3c		36	43[16] (for $R^2 = C_2H_5$)	110°/0.1	—[d]	4.07 (s)	4.10 (for $R^2 = C_2H_5$)[16]
3d		12	85[17] (for $R^2 = C_2H_5$)	—[c]	—[e]	5.90 (d)	5.89 (for $R^2 = C_2H_5$)[17]
3e		51	45-85[18]	105-107°/1	95-97°/0.1[19]	—	—
3f		55	81[19]	104-105° (methanol)	106°[20]	—	—
3g		25	41[21] (for $R^2 = C_2H_5$)	136-137° (1:1 benzene/methanol)	138-139°[21]	4.64 (s)	4.67[21]

[a] Yield of isolated product.
[b] Recorded on a Perkin-Elmer R32 spectrometer.
[c] Purified by column chromatography on silica gel (Merck) eluting with 2:1 benzene/ethyl acetate.
[d] $C_{12}H_{14}O_4$ (222.2) calc. C 64.85 H 6.35; found 64.94 6.23
[e] $C_{13}H_{15}NO_5$ (265.3) calc. C 58.86 H 5.70 N 5.28; found 58.70 5.74 5.09

molar hydrochloric acid (15 ml) are then added to the vigorously stirred mixture, and the organic layer is separated, washed with water, dried with sodium sulphate, and concentrated in vacuo. Dry methanol (25 ml) is added to the residue and the solution is heated under reflux for 2 h and then concentrated in vacuo. The residue is dissolved in dichloromethane (30 ml) and the solution is washed with freshly-prepared saturated aqueous sodium hydrogen carbonate (4 × 50 ml) and with water (50 ml), and then dried with sodium sulphate. Evaporation of the solvent gives the β-keto ester **3** which is purified by distillation or crystallisation.

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