General and Versatile Synthetic Method of Formylacetic Esters[1]

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A convenient and large scale preparation of formylacetates **4** by the reaction of alcohols with formylketene (**2**), readily generated *in situ* from formyl Meldrum's acid **1**, is described.

Acetoacetic esters, important intermediates in organic synthesis, are generally prepared by a base-catalyzed self-condensation of alkyl acetates, known as the acetoacetic ester condensation[2]. Later, a method consisting of a base-catalyzed addition of alcohol to diketene was disclosed[3]. More recently, new syntheses of β-ketoesters were reported[4], which consist of reacting acyl Meldrum's acid with an alcohol. This method is superior to the previous ones not only by its capability of modifying the ester and acyl group but also by the use of neutral conditions throughout the reaction. As for the synthesis of formylacetic esters, however, only the acetoacetic ester condensation is applicable using an appropriate formic ester as the formylation reagent[2]. Due to notable instability of formylacetates (especially under acidic

conditions), the esters prepared by the above method had to be isolated as sodium or pottasium salts and none of physical properties of these esters (in neutral form) have been reported[5].

We wish to report hera a general and versatile method for the synthesis of formylacetic esters starting from formyl Meldrum's acid **1**[6]. The method consists of reacting **1** with an alcohol in benzene (or toluene) under reflux. A mechanism *via* path A is based on our previous finding that **1**, when heated in these solvents, affords formylketene **(2)**[7]. An alternative mechanism, path B, involving an initial alcoholysis of **1** followed by fragmentation of the products **3**, which is essentially the same with the one proposed by Yonemitsu et al[4], is also not excluded at present.

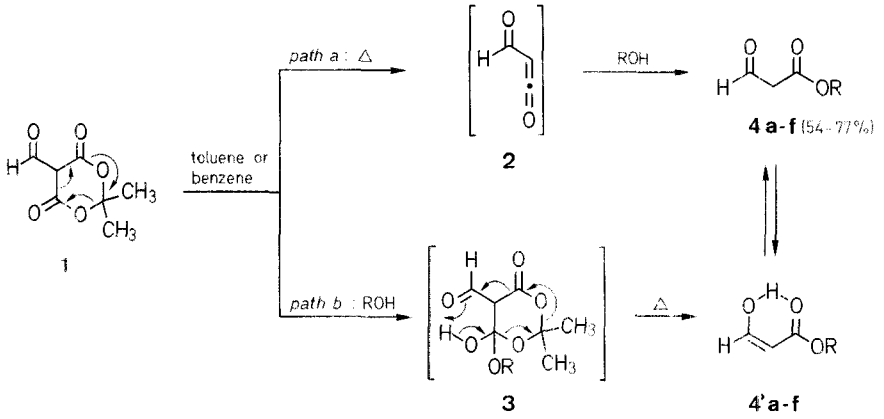
The entire reaction closely resembles to the afore-mentioned method developed by Yonemitsu et al[4] and hence retains its favorable characteristics; a neutral condition throughout, a practically one-pot reaction, and capability of modifying the ester group.

Formylacetic esters 4a–d; General Procedure:
A solution of formyl Meldrum's acid[6] (**1**; 17.2 g, 0.1 mol) and an alcohol (0.12 mol) in dry benzene (200 ml) is refluxed for 90 min. The solvent is evaporated *in vacuo* at room temperature. Distillation of the residue under reduced pressure gives products **4a–d**.

Ethyl Formylacetate **(4a)**; yield: 7.4 g (64%); b.p. 35–50°C/17 torr.

I.R. (CCl_4): ν = 1735 (sh), 1720, 1705 (sh), 1660 cm^{-1}.

Semicarbazone: m.p. 149–150.5°C (Lit.[8], m.p. 147–148°C).



4/4'	R
a	C_2H_5
b	*i*-C_3H_7
c	*t*-C_4H_9
d	$C_6H_5CH_2$
e	O_2N—2—C_6H_4—CH_2
f	CH_2—CCl_3

When **1** is heated in benzene or toluene under reflux in the presence of an alcohol, the reaction takes place smoothly with evolution of carbon dioxide. After the reaction, the solvent is evaporated *in vacuo* and the residue is distilled under reduced pressure to give the corresponding alkyl formylacetate **4**. This reaction can be carried out using 0.1 mole scale of **1** and is extended to the synthesis of *t*-butyl formylacetate **4c** without any difficulty. Compound **4e** could not be purified by distillation due to its high boiling point. However, even in this case, the formation of **4e** is ascertained by semicarbazone formation from the residue. Thus, it is possible to use directly the residue obtained after evaporation of the solvent in the above reactions for further manipulation of **4**. The ^{1}H-NMR data (Table) of products **4** confirm their structures and show that these compounds exist as a mixture of keto **(4)** and enol forms **(4')**.

i-Propyl Formylacetate **(4b)**; yield: 8.58 g (66%); b.p. 30–50°C/8 torr.

I.R. ($CHCl_3$): ν = 1719, 1656 cm^{-1}.

Semicarbazone: m.p. 138–141°C (ethyl acetate).

$C_7H_{13}N_3O_3$ (187.2)	calc.	C 44.91	H 7.00	N 22.45
	found	44.83	6.94	22.63

t-Butyl Formylacetate **(4c)**; yield: 11.1 g (77%); b.p. 35–60°C/11 torr.

I.R. ($CHCl_3$): ν = 1720, 1658 cm^{-1}.

Semicarbazone: m.p. 183–184°C (*n*-hexane/acetone).

$C_8H_{15}N_3O_3$ (201.2)	calc.	C 47.75	N 7.51	N 20.88
	found	47.66	7.47	21.08

Table. ^{1}H-N.M.R. Chemical Shifts [δ, ppm] of Compounds **4a–f**

Compound (Solvent)	4/4' Ratio	4 (pattern, *J*)			4' (pattern, *J*)		Other Signals
		H—C=O	CH_2COO	HOCH=	HOCH=	=CHCOO	
4a (CCl_4)	1 : 2	9.08 (t, 3 Hz)	3.85 (d, 3 Hz)	11.10 (d, 13 Hz)	7.08 (dd, 6 Hz, 13 Hz)	5.02 (d, 6 Hz)	1.30 (t, 3H, J = 7 Hz, CH_3); 4.20 (q, 2H, J = 7 Hz, OCH_2)
4b (CCl_4)	1 : 1	9.70 (t, 2 Hz)	3.24 (d, 2 Hz)	11.48 (d, 12 Hz)	7.03 (dd, 6 Hz, 12 Hz)	4.95 (d, 6 Hz)	1.25 [d, 6H, J = 6Hz, $(CH_3)_2$]; 5.03 [m, 1H, $OCH(CH_3)_2$]
4c (CCl_4)	1 : 1	9.70 (t, 3 Hz)	3.19 (d, 3 Hz)	11.53 (d, 13 Hz)	7.02 (dd, 6 Hz, 13 Hz)	4.90 (d, 6 Hz)	1.50 [s, 9H, $C(CH_3)_3$]
4d (CCl_4)	1 : 1	9.73 (t, 3 Hz)	3.26 (d, 3 Hz)	11.30 (d, 13 Hz)	6.97 (dd, 7 Hz, 13 Hz)	5.07 (d, 7 Hz)	5.12 (s, 2H, OCH_2); 7.32 (s, 5H, C_6H_5)
4e ($CDCl_3$)	3 : 1	9.83 (t, 2 Hz)	3.52 (d, 2 Hz)	11.22 (d, 14 Hz)	[a]	5.22 (d, 6 Hz)	7.08–8.33 (m, $4H_{arom}$)
4f (CCl_4)	1 : 2	9.82 (t, 2 Hz)	3.48 (d, 2 Hz)	10.98 (d, 12 Hz)	7.20 (dd, 6 Hz, 12 Hz)	5.22 (d, 6 Hz)	4.77 (s, 2H, OCH_2 of **4'**); 4.80 (s, 2H, OCH_2 of **4**)

[a] The signals appear in the same region with those of C_6H_4.

Benzyl Formylacetate (**4d**); yield: 3.42 g (65% from 0.03 mol of **1**); b.p. 75–85°C/0.05 torr.

I.R. ($CHCl_3$): ν = 1725, 1660 cm^{-1}.

M.S.: m/e = 150 ($M^+ - CO$).

Semicarbazone: m.p. 147–149°C (*n*-hexane/acetone).

$C_{11}H_{13}N_3O_3$	calc.	C 56.16	H 5.57	N 17.86
(235.1)	found	56.27	5.48	17.88

***o*-Nitrobenzyl Formylacetate (4e):**
A mixture of **1** (860 mg, 5 mmol) and *o*-nitrobenzyl alcohol (765 mg, 5 mmol) is refluxed in dry toluene (12 ml) for 10 min. After evaporation of the solvent *in vacuo*, the residue is triturated with carbon tetrachloride (15 ml) and filtered. Evaporation of solvent *in vacuo* affords **4e** (oil); yield: 600 mg (54%).

M.S.: m/e = 177 ($M^+ - NO_2$).

I.R. ($CHCl_3$): ν = 1740 (sh), 1725, 1665 cm^{-1}.

Semicarbazone: m.p. 159–159.5°C (methanol).

$C_{11}H_{12}N_4O_5$	calc.	C 47.14	H 4.32	N 19.99
(280.2)	found	47.40	4.08	20.15.

2,2,2-Trichloroethyl Formylacetate (4f):
To a refluxing toluene solution (40 ml) of trichloroethanol (2.58 g, 0.04 mol) is added portionwise compound **1** (3.44 g, 0.02 mol). When the addition is complete, the solution is refluxed for additional 15 min. After evaporation of the solvent *in vacuo*, the residue is distilled under reduced pressure to give **4f**; yield: 2.64 g (60%); b.p. 75–81°C/7 torr. I.R. ($CHCl_3$): ν = 1755, 1725, 1675 cm^{-1}.

Semicarbazone: m.p. 143–145°C (ethanol)

$C_6H_8Cl_3N_3O_3$	calc.	C 26.06	H 2.92	Cl 38.45	N 15.20
(276.5)	found	26.24	2.72	38.20	15.56

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[5] All the formylacetic esters **4a–f** prepared readily polymerize even at room temperature. However, in an aprotic solvent (*e.g.*, CCl_4), they can be stored at 0–10°C for a week without any appreciable polymerization. *t*-Butyl formyl acetate is especially stable and can be kept even in neat form at −80°C for a month without any appreciable polymerization.

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