Vilsmeier Formylation of *O*-Silylated Enolates of Carboxylic Esters. A New Method for the Synthesis of α-Formylcarboxylic Esters

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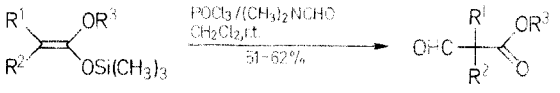
The Vilsmeier formylation of ketene *O*-alkyl *O'*-silyl acetals (*O*-silylated enolates of carboxylic esters) provides α-formylcarboxylic esters in moderate yields.

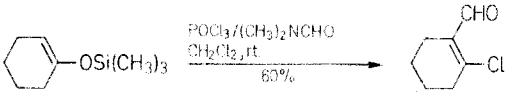
The procedure for the preparation of α-formylcarboxylic esters **(2)** involves ester condensation of carboxylic esters with alkyl formates in the presence of sodium hydride.[1] However, this method suffers from some disadvantages. Thus, removal of the alcohol formed by condensation of the ester with the formate is somewhat difficult, and the yield of **2** is decreased due to self-condensation of the starting carboxylic esters and further

conversion of **2** by the action of sodium hydride, especially in cases in which **2** still has an active H-atom. According to Meyers et al.,[2] the anion of 2-(ethoxycarbonylmethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine can be used to prepare compounds **2** via reaction with alkyl halides and subsequent pH-controlled reduction of the C=N link of the oxazine ring followed by hydrolysis, but the starting dihydro-1,3-oxazine derivative is not easily available. In the oxo reaction of a few 2-alkenoic esters, α-formylation may occur exclusively,[3] depending on the use of $Rh_2Cl_2(CO)_4$ modified by shorter alkanediyl-chain diphosphines such as $(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$ or $HRh(CO)[P(C_6H_5)_3]_3$ together with triphenylphosphine as catalyst. The oxo reaction also seems to provide a relatively direct way to compounds **2**, but it can be used only with 2-alkenoic esters of low molecular weights. The zinc chloride catalyzed-reaction[4] of ketene *O*-alkyl *O'*-silyl acetals (*O*-silylated enolates **1** of alkanoic esters) with dichloromethyl methyl ether also seems to serve the same purpose, but yields are not consistent. A carboxylic ester has been α-formylated[5] using carbon monoxide and sodium methoxide. A brief report describes the α-formylation of 2-substituted alkanoic esters via reaction of the corresponding ketene *O*-methyl *O'*-silyl acetals with *t*-butylimidoacetonitrile in the presence of trimethylsilyl triflate as catalyst, followed by hydrolysis with copper(II) acetate or hydrogen chloride in aqueous methanol.[6] In view of these results, we have studied the reaction of ketene *O*-alkyl *O'*-silyl acetals (**1**) with the Vilsmeier reagent prepared from 2 equivalents of phosphoryl chloride and excess dimethylformamide.[7] The reaction proceeded smoothly at room temperature to afford the α-formylcarboxylic esters **2** in moderate yields. Also, the reaction has been applied to the enol silyl ether of cyclohexanone (**3**) under the same conditions. However, the product obtained was not the expected 2-(hydroxymethylene)-cyclohexanone but 2-chloro-1-formylcyclohexene (**4**) which is accessible[8] by Vilsmeier formylation of cyclohexanone itself.



1a-g **2a-g**

1, 2	R^1	R^2	R^3
a	H	C_2H_5	C_2H_5
b	CH_3	CH_3	C_2H_5
c	CH_3	C_2H_5	CH_3
d	H	i-C_3H_7	C_2H_5
e	C_2H_5	C_2H_5	C_2H_5
f	$-(CH_2)_4-$		CH_3
g	$-(CH_2)_5-$		CH_3



3 **4**

The formation of these products presumably involves electrophilic attack of the Vilsmeier reagent on **1** accompanied by release of trimethylsilyl cation which could combine with either Cl^- or $Cl_2P(O)O^-$. Hydrolysis of the intermediate complex during work-up would then afford the desired ester **2**. The reaction has also been performed by using 4 equivalents of the Vilsmeier reagent; however, the yield of isolated product was thereby not improved. On the other hand, the use of an equivalent amount of Vilsmeier reagent diminished the yields.

The advantages of the present method are that the starting materials are easily available and that performance and work-up are simple.

Table. The Vilsmeier Reaction of Ketene O-Alkyl O'-Silyl Acetals (**1a–g**) or 1-Trimethylsiloxycyclohexene (**3**)

O-Silylated enolate used	Product[a]	Yield[b] (%)	b.p. (°C)/torr	Molecular Formula[c] or b.p. (°C)/torr from Lit.	^{1}H-NMR ($CDCl_3$)[d] δ (ppm)
1a	**2a**	53	66–68/15	71–75/22[3]	*Keto form:* 0.9 (t, 3H); 1.2 (t, 3H); 1.6–1.9 (m, 2H); 3.0–3.2 (m, 1H); 4.1 (q, 2H); 9.6 (d, 1H) *Enol form:* 0.95 (t, 3H); 1.25 (t, 3H); 2.0–2.4 (m, 2H); 4.15 (q, 2H); 6.90 (bs, 1H); 11.2 (d, 1H)
1b	**2b**	52	49–52/10	$C_7H_{12}O_3$ (144.2)	1.23 (t, 3H); 1.28 (s, 6H); 4.13 (q, 2H); 9.57 (s, 1H)
1c	**2c**	52	77–78/30	65–66/17.5[4]	0.88 (t, 3H); 1.29 (s, 3H); 1.7–2.3 (m, 2H); 3.78 (s, 3H); 9.66 (s, 1H)
1d	**2d**	56	85–89/30	$C_8H_{14}O_3$ (158.2)	*Keto form:* 1.03 (d, 6H); 1.22 (t, 3H); 2.0–2.22 (m, 1H); 2.88 (dd, 1H); 4.2 (q, 2H); 9.65 (d, 1H) *Enol form:* 1.08 (d, 6H); 1.24 (t, 3H); 2.2–2.64 (m, 1H); 4.22 (q, 2H); 7.05 (d, 1H); 11.4 (d, 1H)
1e	**2e**	62	96–98/30	82–86/17.5[4]	0.85 (t, 6H); 1.26 (t, 3H); 1.83 (q, 4H); 4.17 (q, 2H); 9.80 (s, 1H)
1f	**2f**	51	104–105/30	92–93/17.5[4]	1.4–1.9 (m, 4H); 1.9–2.3 (m, 4H); 3.70 (s, 3H); 9.56 (s, 1H)
1g	**2g**	53	110–112/30	62–63/2.5[4]	1.2–1.7 (m, 6H); 1.7–2.2 (m, 4H); 3.73 (s, 3H); 9.46 (s, 1H)
3	**4**	60	98–99/18	86–88/10[9]	1.44–1.92 (m, 4H); 2.12–2.4 (m, 2H); 2.44–2.68 (m, 2H); 10.2 (s, 1H)

[a] Some of the products are mixture of stereoisomers.

[b] Yield of product isolated by column chromatography. A small amount of $TiCl_4$ added to the reaction mixture did not improve the yield.

[c] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.26. The results of high-resoultion mass spectrometry and the IR spectra were in accord with the proposed structures:
Ester **2b**. IR (film): ν = 1741, 1730 cm^{-1}.
Ester **2d**. IR (film): ν = 1733 cm^{-1}.

[d] For compounds **2a** and **2d**, enolization is apparent from the ^{1}H-NMR data, the enolization constants being 1 for **2a** and 2 for **2d**.

2-Formylalkanoic Esters 2; General Procedure:
To a stirred, cooled (0–10°C) solution of dimethylformamide (3.0 g, 41 mmol) in dichloromethane (5 ml) is added, dropwise, a solution of phosphoryl chloride (1.57 g, 10.2 mmol) in dichloromethane (3 ml) under nitrogen, and stirring is continued for 30 min at 0–10°C. Then, the ketene *O*-alkyl *O'*-silyl acetal **(1a–g)** or 1-trimethylsiloxycyclohexene **(3)** (5.1 mmol) is added under nitrogen. After the addition is completed the mixture is stirred at room temperature for 15 h during which time it becomes pale yellow. The mixture is then diluted with dichloromethane (15 ml), washed with dilute aqueous sodium hydrogen carbonate (2 × 15 ml) and with saturated sodium chloride solution (20 ml), dried with magnesium sulfate, and concentrated *in vacuo*. The residue is subjected to flash chromatography on silica gel using ethyl acetate/hexane (1:10) as eluent.

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