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A New and Convenient Method of Synthesis of γ-Ketoaldehydes

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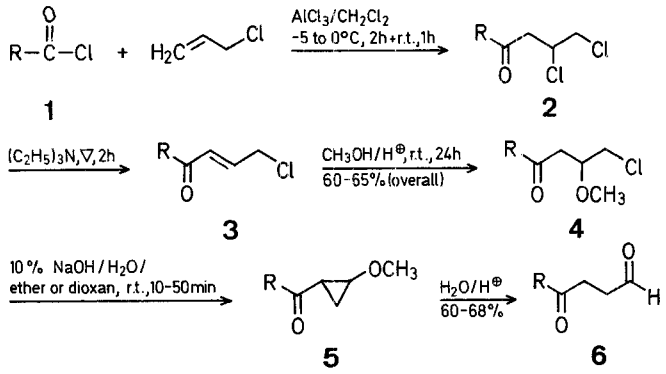
A new synthesis of 4-oxoalkanals starting from acid chlorides and allyl chloride proceeding via alkyl 2,3-dichloropropyl ketones, alkyl 3-chloropropenyl ketones, alkyl 3-chloro-2-methoxypropyl ketones, and 1-alkanoyl-2-methoxycyclopropanes is described.

1,4-Dicarbonyl compounds are important in the synthesis of substituted 2-cyclopentenones, furans, and pyrroles. Much work has been done relating to methods for obtaining 1,4-diketones[1] and γ-ketoaldehydes[2-7], but most of the methods are not convenient with regard to preparative aspects or demand application of special reagents.

In this paper we describe a new method for the synthesis of 4-oxoalkanals **6**. The method consists of the functionalisation of easily accessible β,γ-dichloroketones **2** and subsequent formation of cyclopropanes **5** follwed by cleavage.



1 **2** **3** **4** **5** **6**

1-6	R
a	CH_3
b	C_2H_5
c	n-C_3H_7
d	n-C_4H_9
e	n-C_5H_{11}
f	n-C_6H_{13}

β,γ-Dichloroketones **2** are formed by the condensation of acid chlorides **1** with allyl chloride[8]. Subsequent work up of the ketones **2** with triethylamine, and then with methanol under acidic conditions gives γ-chloro-β-methoxyketones **4** in overall yields of 60–65%. The reactions are carried out without isolating the ketones **2** and **3** from the reaction mixture, because of their lower thermal stability.

Substitution of the chlorine atom in the β-position of **2** by methoxy group leads to preferential 1,3-dehydrochlorination, as compared to the 1,2-elimination process.

Treatment of compound **4** dissolved in ether or dioxan with 10% aqueous solution of sodium hydroxide gives the 2-methoxycyclopropyl ketone **5**[9]. The three-membered rings in **5** are easily opened in a "one-pot procedure" by treatment with dilute hydrochloric acid to form 4-oxoalkanals **6**[10] and their hydrated forms. After dehydration of the latter in the presence of *p*-toluenesulfonic acid, 4-oxoalkanals **6** are isolated.

Alkyl 3-Chloro-2-methoxypropyl Ketones 4a–f; General Procedure: To a stirred solution of acid chloride **1** (0.1 mol) and allyl chloride (15.3 g, 0.2 mol) in dichloromethane (100 ml) is added aluminium chloride (16.0 g, 0.12 mol) in portions over 20 min. The mixture is stirred for 2 h at −5 to 0 °C and for 1 h at room temperature and then poured onto crushed ice (100 g). The organic layer is separated,

Table 1. Alkyl 3-Chloro-2-methoxypropyl Ketones **4a–f** prepared

4	Yield[a] [%]	b.p. [°C]/ torr	Molecular Formula[b]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]
a	64	70–71°/2	$C_6H_{11}ClO_2$ (150.5)	2.13 (s, 3H); 2.63 (d, J = 6 Hz, 2H); 3.33 (s, 3H); 3.52 (d, J = 5 Hz, 2H); 3.6–4.0 (m, 1H)
b	65	76077°/1	$C_7H_{13}ClO_2$ (164.5)	0.90 (t, J = 7 Hz, 3H); 2.53 (d, J = 6 Hz, 2H); 2.56 (q, J = 7 Hz, 2H); 3.31 (s, 3H); 3.48 (d, J = 5 Hz, 2H); 3.5–3.9 (m, 1H)
c	61	90–91°/2	$C_8H_{15}ClO_2$ (178.5)	0.90 (t, J = 7 Hz, 3H); 1.2–1.8 (m, 2H), 2.32 (t, J = 7 Hz, 2H); 2.53 (d, J = 6 Hz, 2H); 3.31 (s, 3H); 3.50 (d, J = 5 Hz, 2H); 3.6–4.0 (m, 1H)
d	60	96–97°/2	$C_9H_{17}ClO_2$ (192.5)	0.92 (t, J = 7 Hz, 3H); 1.2–1.7 (m, 4H); 2.31 (t, J = 7 Hz, 2H); 2.55 (d, J = 6 Hz, 2H); 3.33 (s, 3H); 3.53 (d, J = 5 Hz, 2H); 3.6–4.0 (m, 1H)
e	62	105–106°/2	$C_{10}H_{19}ClO_2$ (204.5)	0.83 (t, J = 7 Hz, 3H); 1.1–1.7 (m, 6H); 2.33 (t, J = 7 Hz, 2H); 2.56 (d, J = 6 Hz, 2H); 3.30 (s, 3H); 3.49 (d, J = 5 Hz, 2H); 3.5–3.9 (m, 1H)
f	61	115–118°/2[c]	$C_{11}H_{21}ClO_2$ (218.5)	0.90 (t, J = 7 Hz, 3H); 1.1–1.7 (m, 8H); 2.34 (t, J = 7 Hz, 2H); 2.56 (d, J = 6 Hz, 2H); 3.31 (s, 3H); 3.50 (d, J = 5 Hz, 2H); 3.6–4.0 (m, 1H)

[a] Yield of isolated product.
[b] All compounds gave satisfactory microanalyses: C ±0.25, H ±0.20.
[c] Compound **4f** is partly decomposed on distillation.

dried with sodium sulfate, filtered and triethylamine (15.1 g, 0.15 mol) is added. The mixture is refluxed for 2 h, cooled to room temperature and washed with dilute hydrochloric acid (100 ml). After evaporating the solvent, methanol (100 ml) and concentrated hydrochloric acid (1 ml) are added to the residue and the mixture is kept at room temperature overnight. The solution is neutralized with saturated aqueous sodium hydrogen carbonate (10 ml), methanol is evaporated in vacuo and the residue is diluted with ether (50 ml). The organic layer is separated, dried with sodium sulfate, the solvent is removed, and the residue distilled in vacuo to give **4** (Table 1).

4-Oxoalkanals 6a–f; General Procedure:
To a stirred solution of ketone **4a, b** (0.1 mol) in ether (100 ml) or ketone **4c–f** (0.1 mol) in dioxan (150 ml), 10% aqueous sodium hydroxide (150 ml) is added and the mixture is stirred at room temperature for 10–50 min until the substrate has fully reacted (G.L.C.). The organic layer is separated and the aqueous phase is extracted with ether (3 × 50 ml). The combined organic layer is shaken up for 3–5 min with 10% hydrochloric acid (30 ml), washed with saturated solution of sodium hydrogen carbonate (100 ml), with water (100 ml) and dried with sodium sulfate. The residue obtained after evaporation of the solvent is diluted with carbon tetrachloride (100 ml), *p*-toluenesulfonic acid (0.1 g) is added and mixture is refluxed for 1 h in a Dean-Stark apparatus. The *p*-toluenesulfonic acid is neutralized with potassium carbonate (0.2 g), the solvent is evaporated, and the residue is distilled in vacuo to afford **6** (Table 2).

Table 2. 4-Oxoalkanals **6a–f** prepared

6	Yield[a] [%]	b.p. [°C]/torr	Lit. b.p. [°C]/torr
a	60	79–80°/20	64–65°/11[6]
b	63	74–75°/12	60–61°/4.5[11]
c	64	87–88°/12	93–94°/15[4]
d	68	83–84°/2	59–60°/1[4]
e	65	94–95°/2	65°/0.1[3]
f	67	104–105°/2	70°/0.25[7]

[a] Yield after distillation, all products gave ^{1}H-N.M.R. spectra which were identical with those of authenic samples.

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