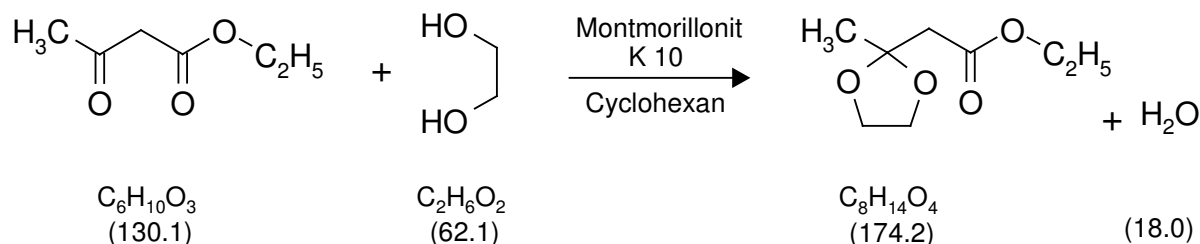


## 2002 Acid catalyzed acetalisation of acetoacetic acid ethyl ester with ethanediol to the corresponding 1,3-dioxolane



### Classification

#### Reaction types and substance classes

reaction of the carbonyl group in ketones, acetalisation  
ketone, alcohol, acetal, protecting group, acid catalyst

#### Work methods

removal of water by azeotropic distillation, stirring with KPG stirrer, filtering, evaporating with rotary evaporator, distilling under reduced pressure, fractionating column distillation, rectifying, heating with oil bath, stirring with magnetic stir bar

for batch scale 10 mmol:

stirring with magnetic stirrer instead of KPG-stirrer, heating under reflux with Soxhlet extractor instead of water separator, no distillation over a column

### Instruction (batch scale 200 mmol)

#### Equipment

500 mL three-neck flask, 100 mL round bottom flask, water separator, reflux condenser, KPG stirrer, hot plate, distillation apparatus or rotary evaporator, 30 cm Vigreux column with vacuum jacket (preferably NS 29/32), vacuum column head, vacuum pump, oil bath

#### Substances

ethanediol (bp 198 °C)	14.9 g (13.5 mL, 240 mmol)
acetoacetic acid ethyl ester (bp 180 °C)	26.0 g (25.2 mL, 200 mmol)
cyclohexane (bp 81 °C)	220 mL
Montmorillonit K 10	12.0 g
for a derivative:	
2,4-dinitrophenylhydrazine (mp 203 °C)	2.0 g
conc. H <sub>2</sub> SO <sub>4</sub>	10 mL
ethanol (bp 78 °C)	50 mL

**Reaction**

200 mL cyclohexane, 26.0 g (25.2 mL, 200 mmol) acetoacetic acid ethyl ester, 14.9 g (13.4 mL, 240 mmol) ethanediol and 12.0 g Montmorillonit K 10 are filled in a dry 500 mL three-neck flask with KPG stirrer, water separator and reflux condenser. The mixture is heated under stirring with a KPG stirrer at the water separator under reflux, until no more water separates (about 3 h, separated aqueous phase 6.8 mL).

**Work up**

After cooling down to room temperature, the suspension is filtered over a folded filter into a 500 mL round bottom flask and the residue is washed with 20 mL cyclohexane. The solvent is distilled at normal pressure or evaporated at a rotary evaporator with a weak vacuum (235 hPa, bath temperature 50 °C). As crude product remains a light-yellow oily residue.

Crude yield: 26.1 g; GC-purity 92% (see analytics)

The residue is transferred into a 100 mL round bottom flask and fractional distilled at about 14 hPa over a 30 cm Vigreux column with vacuum jacket and a vacuum column head.

Distillation protocol (example):

Fraction	Head temperature (°C)	Pressure (hPa)	Oil bath temperature (°C)	Mass (g)	GC-purity (%) <sup>*)</sup>
1	until 77	8.1	122	0.453	41.6
2	78-85	12.0	130	0.823	48.9
3	85-86	9.1-11.0	133	1.611	75.1
4	86-87	9.0-11.0	137	4.179	90.4
5	86-87	9.0-10.0	137	7.001	93.8
6	86-87	8.0-9.0	140	8.815	98.7
7	86-76	8.0	140-160	1.314	98.7

\*) Here percent product for each fraction are listed, the rest is predominantly acetoacetic acid ethyl ester.

Distillation residue: 1.85 g

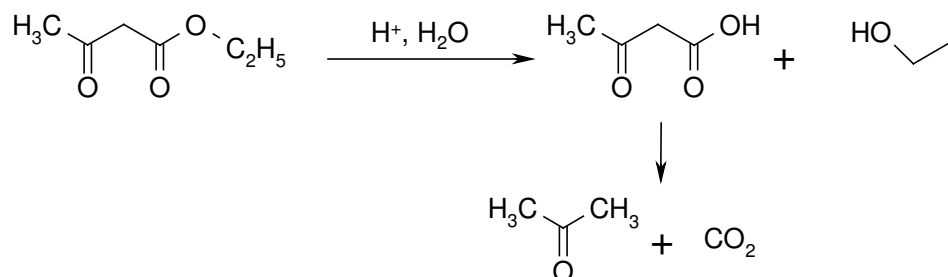
Yield (Fractions 4-7): 21.3 g (122 mmol, 61%); bp 86-87 °C (8-10 hPa); colourless liquid

**Comments**

The KPG stirrer should not be replaced through a magnetic stirrer, because through the water contents of the solution the Montmorillonit K 10 agglomerates at the beginning of the reaction: An insufficient stirring of the mixture might cause strong delays in boiling.

The yield of the reaction is not very high. According to the mass balance between educts and isolated product it is likely that light-volatile side products are formed and at the latest during distillation of the solvent distill over too and then get lost.

Possible side reaction:



Argumentation for this:

$\text{CO}_2$  can be detected if the reflux condenser is connected with a wash bottle with saturated  $\text{Ba}(\text{OH})_2$  solution and a second wash bottle guarantees, that no  $\text{CO}_2$  from the outside air streams into the first wash bottle. During reaction a barium carbonate precipitation is formed.

The aqueous phase, which is collected in the water separator, is almost twice as much as expected for the acetalisation reaction (6.8 instead of 3.6 mL).

If a sample of the aqueous phase is shaken out with  $\text{CDCl}_3$  and a  $^1\text{H}$  NMR spectrum is made from the  $\text{CDCl}_3$ -solution, signals for acetone and ethanol are found.

In the distilled cyclohexane, mainly in the first fractions, also acetone and ethanol are detected with GC.

From the aqueous phase in the water separator the 2,4-dinitrophenylhydrazone of acetone can be precipitated. Procedure:

To 2 g of 2,4-dinitrophenylhydrazine 10 mL conc.  $\text{H}_2\text{SO}_4$ , are added and then under shaking and dropwise 14 mL  $\text{H}_2\text{O}$ . The still warm solution is diluted with 50 mL ethanol. 50 mL of this solution are mixed with about 2 mL of the separated aqueous phase (from water separator). A fine-crystalline orange solid precipitates within a few minutes. If not, a small amount of water is added dropwise until first crystals are formed. The precipitation is sucked off and dried, mp 115–117 °C (without recrystallization).

### Waste management

#### Recycling

The cyclohexane of the reaction solution is collected and redistilled, however, it might contain - depending on the quality of the distillation - acetone and ethanol.

Montmorillonit K 10 can be recycled after drying.

**Waste disposal**

Waste	Disposal
cyclohexane, if not recycled	organic solvents, halogen free
Montmorillonit K 10	solid waste, free from mercury
aqueous phase from the water separator	solvent water mixtures, halogen free
distillation residue	organic solvents, halogen free
mother liquor of 2,4 dinitrophenylhydrazone	solvent water mixtures, halogen free

**Time**

About 7 hours

**Break**

After filtering off the Montmorillonit

After distillation of the solvent

**Degree of difficulty**

Medium

**Instruction (batch scale 1 mol)****Equipment**

1 L three-neck flask, 250 mL round bottom flask, water separator, reflux condenser, KPG stirrer, hot plate, oil bath, rotary evaporator, 30 cm Vigreux column with vacuum jacket (preferably NS 29/32), vacuum column head, vacuum pump

**Substances**

ethanediol (bp 198 °C)	74.5 g (67.7 mL, 1.20 mol)
acetoacetic acid ethyl ester (bp 180 °C)	130 g (126 mL, 1.00 mol)
cyclohexane (bp 81 °C)	650 mL
Montmorillonit K 10	60 g
for a derivative:	
2,4-dinitrophenylhydrazine (mp 203 °C)	2.0 g
conc. H <sub>2</sub> SO <sub>4</sub>	10 mL
ethanol (bp 78 °C)	50 mL

**Reaction**

600 mL cyclohexane, 130 g (126 mL, 1.00 mol) acetoacetic acid ethyl ester, 74.5 g (67.7 mL, 1.20 mol) ethanediol and 60 g Montmorillonit K 10 are filled in a dry 1 L three-neck flask with KPG-stirrer, water separator and reflux condenser. The mixture is heated under stirring with a KPG-stirrer at the water separator under reflux, until no more water separates (about 13 h, separated aqueous phase 34 mL).

**Work up**

After cooling down to room temperature, the suspension is filtered over a folded filter into a 1 L round bottom flask and the residue is washed with 50 mL cyclohexane. The solvent is evaporated at a rotary evaporator with a weak vacuum (235 hPa, bath temperature 50 °C). As crude product remains a light-yellow oily residue.

Crude yield: 132 g; GC-purity 91% (see analytics)

The crude product is transferred into a 250 mL round bottom flask and fractional distilled at about 14 hPa over a 30 cm Vigreux column with vacuum jacket and a vacuum column head.

Distillation protocol (example):

Fraction	Head temperature (°C)	Pressure (hPa)	Oil bath temperature (°C)	Mass (g)	GC-purity (%) <sup>*)</sup>
1	until 80	9.7-10.0	bis 126	1.29	53.6
2	77-82	8.4-10.0	126-130	2.43	61.1
3	83-88	12.0-13.0	125	6.71	71.1
4	88-89	11.0-12.0	125-130	5.15	79.6
5	87-88	9.4-11.0	132	14.16	87.7
6	86-87	8.9-9.1	132	6.78	92.3
7	86	8.4-8.6	133	11.15	95.5
8	86-89	8.4-10.0	133	9.72	97.5
9	87-88	8.1-8.5	133	14.88	98.4
10	89	9.1-9.5	133	15.22	98.9
11	86-88	8.3-9.1	133	15.37	99.2
12	89	9.0	133	14.70	99.0
13	89	9.0	133	9.52	98.2
14	87-88	8.4	133-155	1.94	96.4

\*) Here percent product for each fraction are listed, the rest is predominantly acetoacetic acid ethyl ester.

Distillation residue: 2.35 g

Yield (fractions 9-13): 69.7 g (400 mmol, 40%)

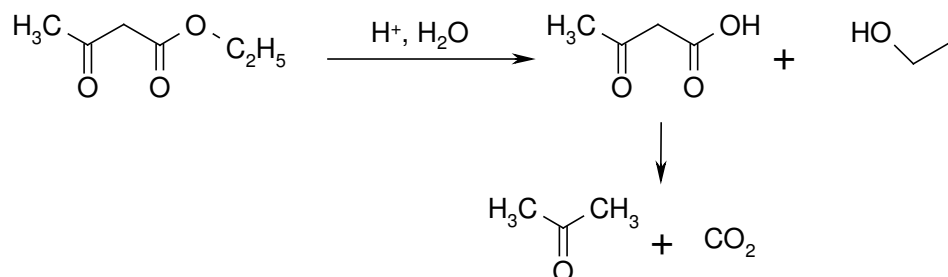
Yield (fractions 5 – 8): 41.8 g (240 mmol, 24%)

**Comments**

The KPG stirrer must not be replaced through a magnetic stirrer in this large scale batch, because through the solid in the flask an insufficient stirring of the mixture causes strong delays in boiling.

The yield of the reaction is not very high. According to the mass balance between educts and isolated product it is likely that light-volatile side products are formed and at the latest during distillation of the solvent distill over too and then get lost.

Possible side reaction:



Argumentation for this:

$\text{CO}_2$  can be detected if the reflux condenser is connected with a wash bottle with saturated  $\text{Ba}(\text{OH})_2$  solution and a second wash bottle guarantees that no  $\text{CO}_2$  from the outside air streams into the first wash bottle. During reaction a barium carbonate precipitation is formed.

The aqueous phase which is collected in the water separator is almost twice as much as expected for the acetalisation reaction (34 instead of 18 mL).

If a sample of the aqueous phase is shaken out with  $\text{CDCl}_3$  and a  $^1\text{H}$  NMR spectrum is made from the  $\text{CDCl}_3$ -solution, signals for acetone and ethanol are found.

In the distilled cyclohexane, mainly in the first fractions, also acetone and ethanol are detected with GC.

From the aqueous phase in the water separator the 2,4-dinitrophenylhydrazone of acetone can be precipitated. Procedure:

To 2 g of 2,4-dinitrophenylhydrazine 10 mL conc.  $\text{H}_2\text{SO}_4$ , are added and then under shaking and dropwise 14 mL  $\text{H}_2\text{O}$ . The still warm solution is diluted with 50 mL ethanol. 50 mL of this solution are mixed with about 2 mL of the separated aqueous phase (from water separator). A fine-crystalline orange solid precipitates within a few minutes. If not, a small amount of water is added dropwise until first crystals are formed. The precipitation is sucked off and dried, mp 115–117 °C (without recrystallization).

### Waste management

#### Recycling

The cyclohexane of the reaction solution is collected and redistilled, however, it might contain - depending on the quality of the distillation - acetone and ethanol.

Montmorillonit K 10 can be recycled after drying.

**Waste disposal**

Waste	Disposal
cyclohexane, if not recycled	organic solvents, halogen free
Montmorillonit K 10	solid waste, free from mercury
aqueous phase from the water separator	solvent water mixtures, halogen free
distillation residue	organic solvents, halogen free
mother liquor of the 2,4 dinitrophenylhydrazone	solvent water mixtures, halogen free

**Time**

About 20 hours

**Break**

After filtering off the Montmorillonit from the reaction solution

After distillation of the solvent

**Degree of difficulty**

Medium

**Instruction (batch scale 10 mmol)****Equipment**

100 mL round bottom flask, 30 mL Soxhlet extractor with extraction cone, reflux condenser, heatable magnetic stirrer, magnetic stir bar, oil bath, microdistillation apparatus, vacuum pump

**Substances**

ethanediol (bp 198 °C)	745 mg (0.677 mL, 12.0 mmol)
acetoacetic acid ethyl ester (bp 180 °C)	1.30 g (1.26 mL, 10.0 mmol)
cyclohexane (bp 81 °C)	60.0 mL
Montmorillonit K 10	600 mg
molecular sieve 4 Å	5.0 g

**Reaction**

50 mL cyclohexane, 1.30 g (1.26 mL, 10.0 mmol) acetoacetic acid ethyl ester, 745 mg (0.677 mL, 12.0 mmol) ethanediol and 600 g Montmorillonit K 10 are filled in a dry 100 mL three-neck flask with magnetic stirrer, 30 mL Soxhlet extractor and reflux condenser. 5.0 g molecular sieve are filled in the extraction cone of the Soxhlet extractor in order to bind the water formed during reaction. The mixture is heated under stirring for 3 hours under reflux.

**Work up**

After cooling down to room temperature, the suspension is filtered over a folded filter into a 100 mL round bottom flask and the residue is washed with 10 mL cyclohexane. The solvent is distilled off at normal pressure. A colourless oily residue remains.

Crude yield: 1.13 g

The residue is distilled in a microdistillation apparatus at about 14 hPa.

Yield: about 1.0 g (5.7 mmol, 57%); bp 85-89 °C (12-14 hPa)

The yield depends very much on the distillation apparatus and the personal skills.

### **Waste management**

#### **Recycling**

The molecular sieve can be regenerated.

#### **Waste disposal**

<b>Waste</b>	<b>Disposal</b>
cyclohexane	organic solvents, halogen free
Montmorillonit K 10	solid waste, free from mercury
distillation residue	organic solvents, halogen free

#### **Time**

About 5 hours

#### **Break**

After filtering off the Montmorillonit from reaction solution

After distillation of the solvent

#### **Degree of difficulty**

Medium

## **Analytcs**

### **Reaction monitoring**

GC can be used for monitoring, the large batches can also be controlled through the volume of the separated aqueous phase.

If a reaction monitoring with GC is planned, one should use a two- or three-neck flask for the reaction, so that the samples can be taken through the second neck.

For each sample the reaction mixture is allowed to cool down (through lowering the lab jack with the oilbath), until the solution stops boiling. Using a pipette one takes about 3 mL from the solution and fills it through a paper filter into a small round bottom flask. The solvent is evaporated at a rotary evaporator. The residue is analyzed without addition of a solvent for acetoacetic acid ester and product. For detection of ethanol and acetone in the reaction solution, a sample is taken as described above, filtered and injected.



## GC-conditions:

column: Zebron ZB-1, length 15 m, internal diameter 0.25 mm, film 0.25  $\mu\text{m}$ ,  
(Phenomenex, Torrance, CA, USA)

inlet: injector temperature 250 °C; split injection; injected volume 0.02  $\mu\text{L}$  (without solvent)  
A decomposition of the substances in the injector could be excluded through a test with an  
injector temperature of only 150 °C.

carrier gas: He, pre-column pressure 90 kPa

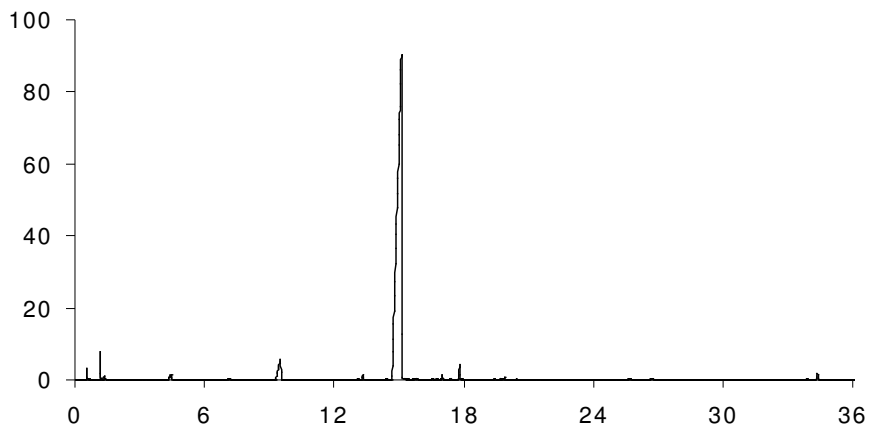
oven: start temperature 30 °C (8 min), 10 °C/min at 150 °C (10 min), 10 °C/min at 200 °C (10 min).  
The low start temperature is necessary to prove acetone and ethanol clearly.

detector: FID, 250 °C,  $\text{H}_2$  33.9 mL/min; synth. air 322 mL/min; make-up-gas  $\text{N}_2$ , flow 15.0 mL/min  
(59 kPa)

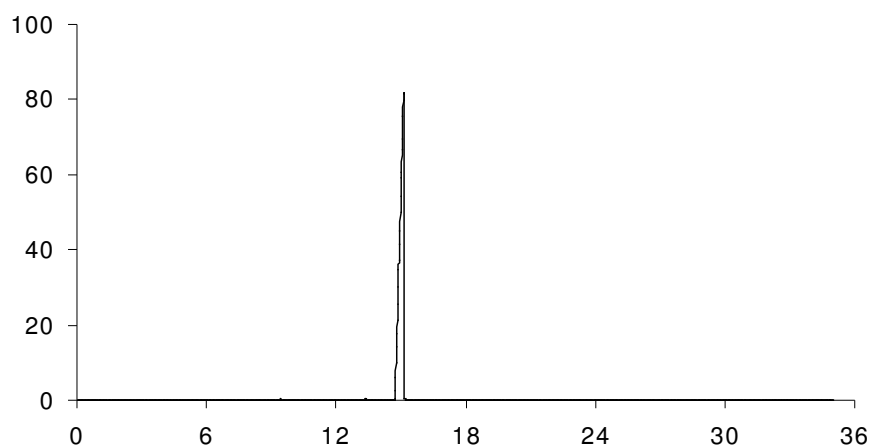
integration: integrator 4290 (Thermo Separation Products)

Percent concentration was calculated from peak areas.

## GC of the crude product

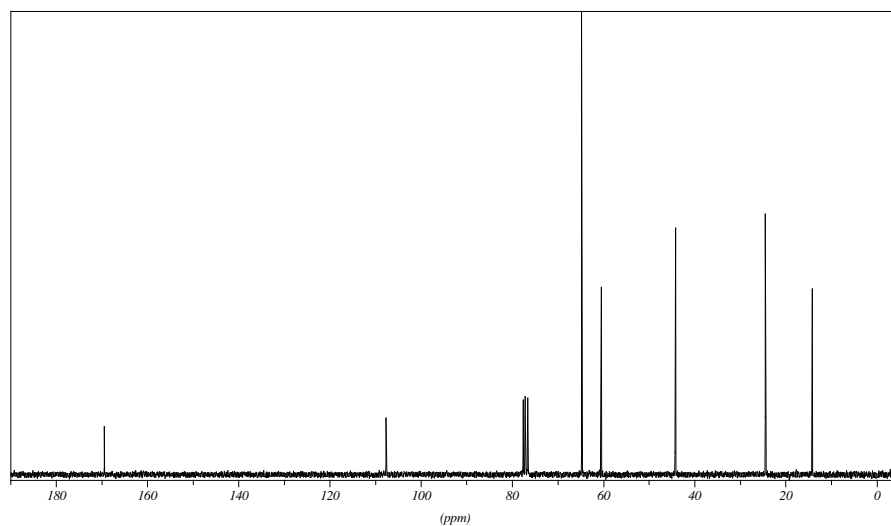


Retention time (min)	Substance	Peak area %
0.5	ethanol	0.4
0.6	acetone	0.1
1.2	cyclohexane	1.1
9.5	acetoacetic ester	3.2
15.1	product	91.7
others	not identified	3.5

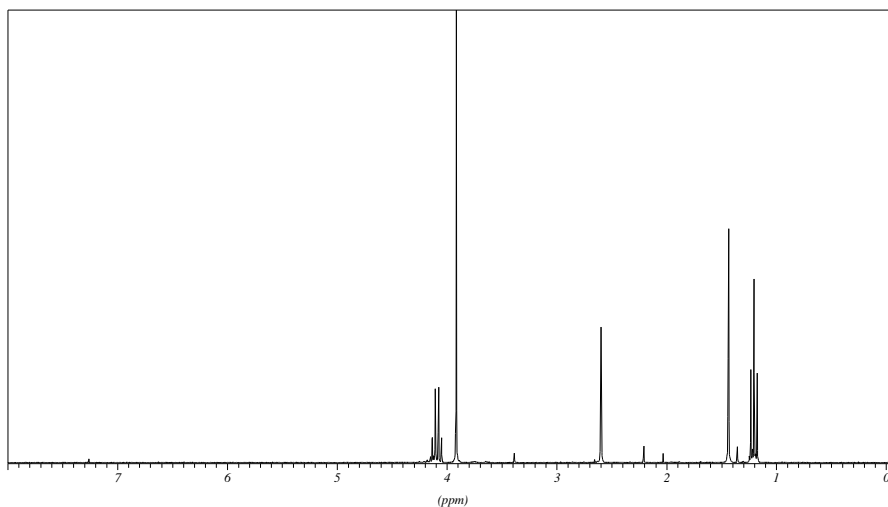
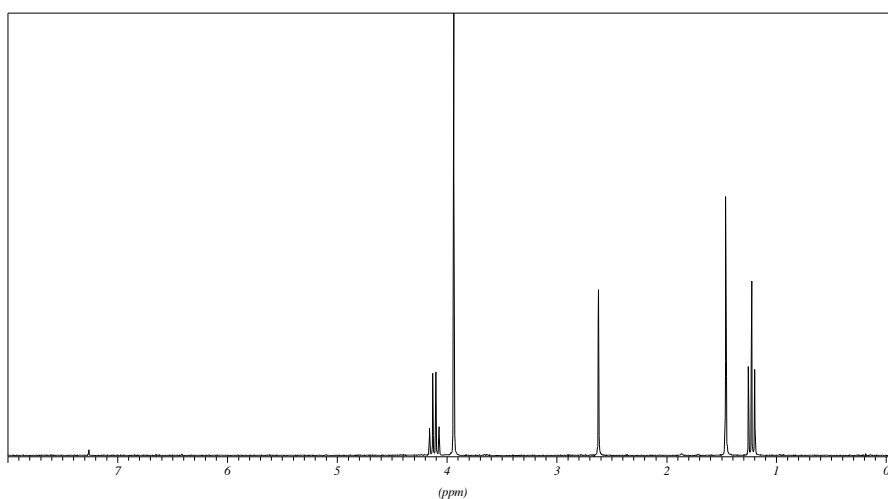
**GC of the pure product**

Retention time (min)	Substance	Peak area %
15.1	product	99.6

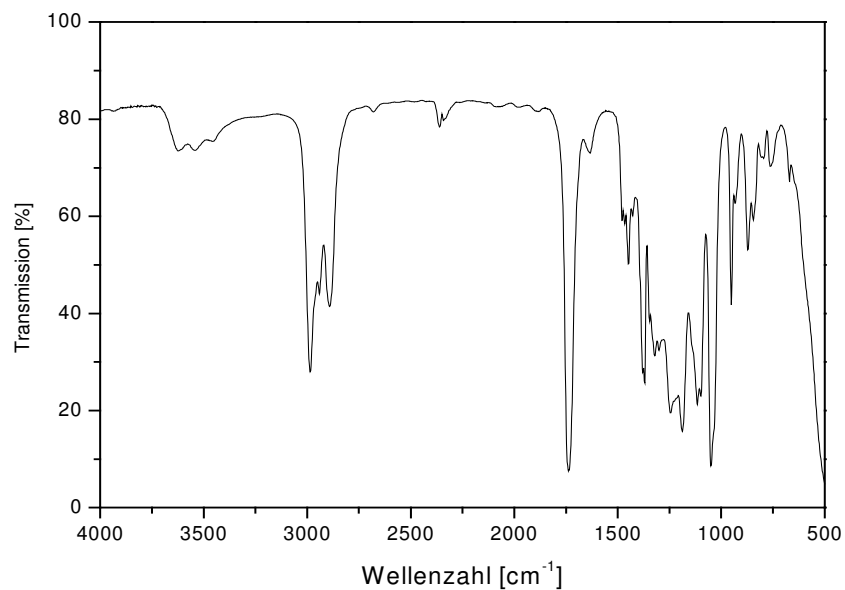
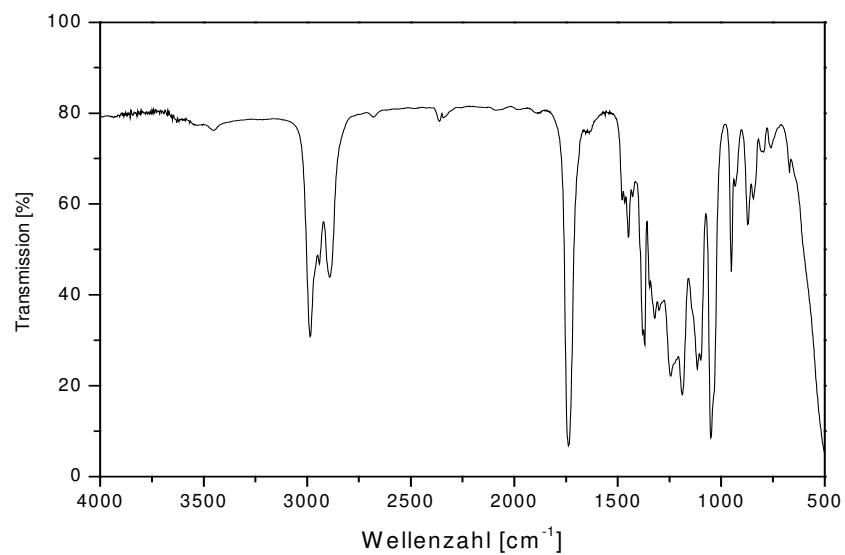
The GC of the distillation residues still shows 41% product besides unidentified substances with higher retention times.

**<sup>13</sup>C NMR spectrum of the pure product (250 MHz, CDCl<sub>3</sub>)**

$\delta$ (ppm)	Assignment
14.1	- CH <sub>2</sub> - CH <sub>3</sub>
24.5	CH <sub>3</sub> - C(dioxolan)
44.2	- CH <sub>2</sub> - CO -
60.5	- O - CH <sub>2</sub> - CH <sub>3</sub>
64.7	- O - CH <sub>2</sub> - CH <sub>2</sub> - O -
107.6	C (quart.) dioxolanring
169.4	CO - O -
76.5-77.5	solvent

**$^1\text{H}$  NMR spectrum of the crude product (250 MHz,  $\text{CDCl}_3$ )** **$^1\text{H}$  NMR spectrum of the pure product (250 MHz,  $\text{CDCl}_3$ )**

$\delta$ (ppm)	Multiplicity	Number of H	Assignment
1.22	t	3	$-\text{CH}_2-\text{CH}_3$
1.46	s	3	$\text{CH}_3-\text{C}(\text{dioxolan})$
2.62	s	2	$-\text{CH}_2-\text{CO}-$
3.93	s	4	$-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$
4.11	q	2	$-\text{O}-\text{CH}_2-\text{CH}_3$

**IR spectrum of the crude product (film)****IR spectrum of the pure product (film)**

(cm <sup>-1</sup> )	Assignment
2984	C – H – valence, alkane
2894	C – H – valence, alkane
1738	C = O – valence, ester