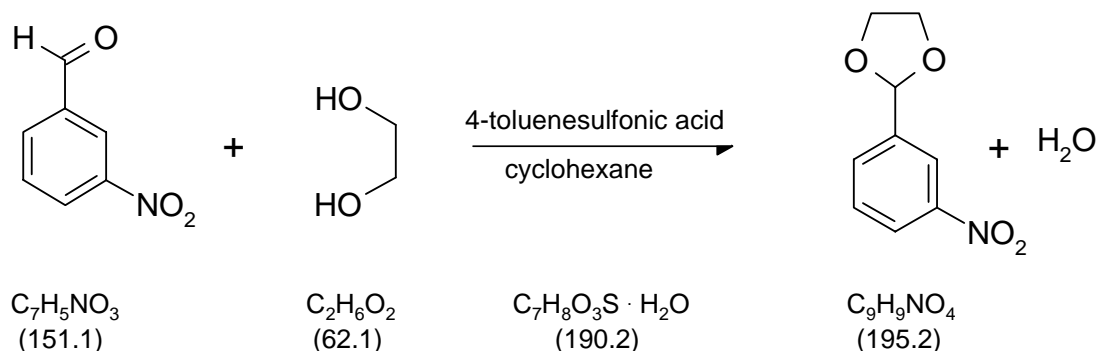


## 2003 Acid catalyzed acetalisation of 3-nitrobenzaldehyde with ethanediol to the correspondent 1,3-dioxolane



### Classification

#### Reaction types and substance classes

reaction of the carbonyl group in aldehydes, acetalisation  
aldehyde, acetal, alcohol, protecting group, acid catalyst

#### Work methods

removal of water by azeotropic distillation, heating under reflux with Soxhlet extractor (for 10 mmol batch scale), stirring with magnetic stir bar, evaporating with rotary evaporator, shaking out, extracting, recrystallizing, filtering, heating with oil bath

### Instruction (batch scale 100 mmol)

#### Equipment

500 mL round-bottom flask, water separator, reflux condenser, heatable magnetic stirrer with magnetic stir bar, separating funnel, rotary evaporator, suction flask, suction filter, desiccator, oil bath

#### Substances

3-nitrobenzaldehyde (mp 58 °C; product from NOP-Nr. 1003)	15.1 g (100 mmol)
ethanediol (bp 198 °C)	6.83 g (6.20 mL, 110 mmol)
4-toluenesulfonic acid monohydrate (mp 103-105 °C)	190 mg (1.00 mmol)
cyclohexane (bp 81 °C)	200 mL
<i>tert</i> -butyl methyl ether (bp 55 °C)	200 mL
sodium disulfite	about 13 g (for 20 mL saturated aqueous NaHSO <sub>3</sub> -solution)
sodium sulfate for drying	about 5 g
cyclohexane (bp 81 °C) for recrystallization	about 30 mL
<i>tert</i> -butyl methyl ether (bp 55 °C) for recrystallization	about 30 mL

### Reaction

15.1 g (100 mmol) 3-nitrobenzaldehyde, 6.83 g (6.20 mL, 110 mmol) ethanediol and 1.00 g (5.30 mmol) 4-toluenesulfonic acid monohydrate are dissolved in 200 mL cyclohexane in a dry 500 mL round-bottom flask equipped with a magnetic stirring bar, water separator and reflux condenser. The reaction mixture is refluxed until no more water is collected in the water separator (approx. 2-3 h).

### Work up

The hot reaction mixture is decanted into another 500 mL round-bottom flask to separate it from an oily sediment which has separated at the bottom of the reaction vessel (about 200 mg). The sediment consists predominantly of product, starting material and 4-toluenesulfonic acid (<sup>1</sup>H-NMR spectrum). The solvent of the decanted solution is directly removed with a rotary evaporator. A yellow crystalline solid remains as crude product.

Crude yield: 19.7 g; mp 50-52 °C; purity according to GC 95% acetal in addition to 4% aldehyde

In order to remove unreacted aldehyde as hydrogensulfite adduct the crude product is dissolved in 200 mL *tert*-butyl methyl ether and extracted once with 20 mL saturated aqueous sodium hydrogensulfite solution. The organic phase is dried over sodium sulfate, the sodium sulfate is removed by filtration and the solvent is evaporated with a rotary evaporator to yield a nearly colorless crystalline residue.

Yield: 17.9 g; (91.7 mmol, 92%); mp 57 – 58 °C; purity according to GC more than 99%.

The product is for most uses pure enough. If further purification is required, recrystallization from a solvent mixture of cyclohexane/*tert*-butyl methyl ether in a ratio of 1:1 (approximately 45 mL) can be carried out. The solution should be allowed to stand covered at room temperature until crystals form (if needed 1 to 2 days). If the solution is cooled quickly in an ice bath, only an oil generally forms. After cooling for a short time in an ice bath, the crystals are filtered and dried until constant mass is achieved in a desiccator at reduced pressure.

Yield: 15.9 g (81.5 mmol; 82%); mp 57 – 58 °C; colorless crystals; purity according to GC more than 99 % (see analytics).

The product can also be recrystallized from a very small amount of ethanol (13 mL), however with much poorer yield.

### Comments

The decanted reaction mixture as well as the extracted *tert*-butyl methyl ether solution should not be allowed to stand too long before evaporation of the solvent, as traces of acid and water present may cause the cleavage of the acetal. The solution should also not be heated longer than necessary during recrystallization.

The collected volume of water in the water separator may be larger than the theoretical amount, because of some water content of the 4-toluenesulfonic acid or other chemicals.

**Waste management****Recycling**

The cyclohexane of the reaction mixture and the *tert*-butyl methyl ether are collected and redistilled.

**Waste disposal**

Waste	Disposal
aqueous phase from water separator	solvent water mixtures, halogen free
aqueous phase from shaking out	solvent water mixtures, halogen free
residue from the reaction flask	dissolve in a small amount of acetone, then: organic solvents, halogen free
mother liquor from recrystallization	organic solvents, halogen free
sodium sulfate	solid waste, free from mercury

**Time**

Approximately 5 hours including work up

**Break**

After evaporation of the cyclohexane from the reaction solution

**Degree of difficulty**

Easy

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

500 mL round-bottom flask, 30 mL Soxhlet extractor with extraction sleeve, reflux condenser, heatable magnetic stirrer with magnetic stir bar, separating funnel, rotary evaporator, suction flask, suction filter, desiccator, oil bath

**Substances**

3-nitrobenzaldehyde (mp 58 °C; product from NOP-Nr. 1003)	1.51 g (10.0 mmol)
ethanediol (bp 198 °C)	683 mg (0.620 mL, 11.0 mmol)
4-toluenesulfonic acid monohydrate (mp 103-105 °C)	19 mg (0.10 mmol)
cyclohexane (bp 81 °C)	50 mL
molecular sieve 4 Å	10 g
<i>tert</i> -butyl methyl ether (bp 55 °C)	20 mL
sodium disulfite	about 3 g (for 5 mL saturated aqueous NaHSO <sub>3</sub> -solution)
sodium sulfate for drying	about 1 g
cyclohexane (bp 81 °C) for recrystallization	about 3 mL
<i>tert</i> -butyl methyl ether (bp 55 °C) for recrystallization	about 3 mL

## Reaction

The reaction apparatus consists of a dry 100 mL round-bottom flask with a magnetic stir bar and a 30 mL soxhlet extraction unit with a reflux condenser. The extraction sleeve in the soxhlet extraction apparatus is filled with 10 g molecular sieve 4 Å, in order to trap the water produced during the reaction. 1.51 g (10.0 mmol) 3-Nitrobenzaldehyde and 50 mL cyclohexane are placed into the reaction flask, to which 683 mg (0.620 mL, 11.0 mmol) ethanediol and 19 mg (0.10 mmol) 4-toluenesulfonic acid monohydrate is added. The reaction mixture is allowed to stir under reflux for 2 hours.

## Work up

The hot reaction mixture is decanted from the minimal amount of oily sediment into a 100 mL round-bottom flask. The sediment consists predominantly of product, starting material and the 4-toluenesulfonic acid (<sup>1</sup>H-NMR spectrum). The solvent is directly evaporated from the decanted solution. A yellow crystalline solid remains as crude product.

Crude yield: 1.96 g; mp 50-52 °C; purity according to GC 95% acetal, in addition to 4% aldehyde

In order to remove unreacted aldehyde as sodium hydrogensulfite adduct, the crude product is dissolved in 20 mL *tert*-butyl methyl ether and extracted once with 5 mL saturated sodium hydrogensulfite solution. Once the organic phase has been dried over sodium sulfate and the drying agent has been filtered off, the solvent is evaporated. An almost colourless crystalline solid remains. This product crystallizes as almost colourless needles.

Yield: 1.82 g (9.32 mmol, 93%); mp 57-58 °C; purity according to GC over 99%

The product is for most uses pure enough. If further purification is required, recrystallization from a solvent mixture of cyclohexane/*tert*-butyl methyl ether in a ratio of 1:1 (approximately 4.5 mL) can be carried out. The solution should be allowed to stand covered at room temperature until crystals form (if needed 1 to 2 days). If the solution is cooled quickly in an ice bath, only an oil generally forms. After cooling for a short time in an ice bath, the crystals are filtered and dried until constant mass is achieved in a desiccator at reduced pressure.

Yield: 1.60 g (8.20 mmol, 82%); mp 57-58 °C; colourless, shiny crystalline platelets; purity according to GC > 99% (see analytics)

The product can also be recrystallized from a very small amount of ethanol (amount 1.5 mL), however with much poorer yields.

## Comments

The decanted reaction mixture as well as the extracted *tert*-butyl methyl ether solution should not be allowed to stand too long before evaporation of the solvent, as traces of acid and water present may cause the cleavage of the acetal. The solution should also not be heated longer than necessary during recrystallization.

**Waste management****Recycling**

The cyclohexane of the reaction mixture and the *tert*-butyl methyl ether are collected and redistilled. The molecular sieve can be regenerated.

**Waste disposal**

Waste	Disposal
aqueous phase from shaking out	solvent water mixtures, halogen free
residue from the reaction flask	dissolve in a small amount of acetone, then: organic solvents, halogen free
mother liquor from recrystallization	organic solvents, halogen free
sodium sulfate	solid waste, free from mercury

**Time**

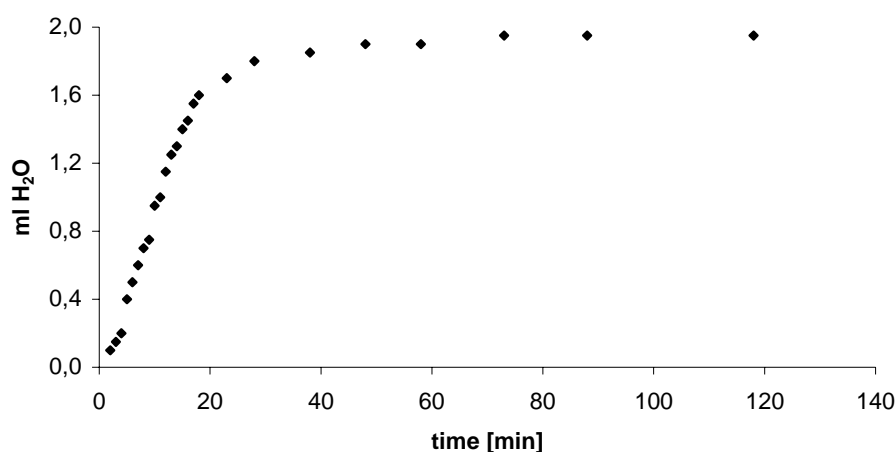
Approximately 5 hours including work up

**Break**

After evaporation of the cyclohexane from the reaction solution

**Degree of difficulty**

Easy

**Analytcs****Reaction monitoring using the amount of collected reaction water**

Batch scale: 100 mmol

Start of reaction water collection is set as point 0 on the reaction coordinate.

The time needed for this reaction varies with the rate heating the reaction to the reaction temperature and the time needed for distillation. Extension of the reaction time to 18 hours does not improve the reaction conversion.

### Reaction monitoring by TLC

Monitoring by TLC is not suitable for this reaction, because remaining small amounts of aldehyde even at the end of the reaction. A satisfactory separation of aldehyde and dioxolane could not be achieved in typical organic solvents.

### Reaction monitoring by GC

Sample preparation for 100 mmol reaction scale:

For reaction monitoring use a three-neck flask as reaction vessel instead of a single-neck flask to comfortably draw samples using the additional flask openings. In order to generate enough measurements, even at low turnovers before the reaction mixture is brought to reflux, the reaction mixture should be brought very slowly to reflux (in approximately 40-50 minutes). The first sample can be taken as soon as the 3-nitrobenzaldehyde has completely dissolved under mild heating.

Prior to starting the reaction, 2 mL of *tert*-butyl methyl ether is filled into the provided preparatory vials.

For the collection of each sample do the following: The oil bath is lowered. As soon as the solution is no longer at reflux, the stirrer is stopped and then one waits approximately 1 minute until the not completely soluble components of the reaction mixture sediment. Using a pipette, a 2 mL sample of the solution is taken via one of the flask openings and placed into a sample vial. The solution contained in the sample vial is then once more carefully taken up in a pipette so as to redissolve any freshly precipitated substance, before being transferred back into the sample vial. The sample is immediately cooled down in an ice bath and then placed into the freezer until GC measurement.

The reaction vessel is heated under stirring until the next sample is taken.

If the GC measurement cannot be carried out within 24 hours, one should transfer the sample into a small round-bottom flask, evaporate the solvent with a rotary evaporator, and then dissolve the precipitate in 4 mL *tert*-butyl methyl ether prior to measurement.

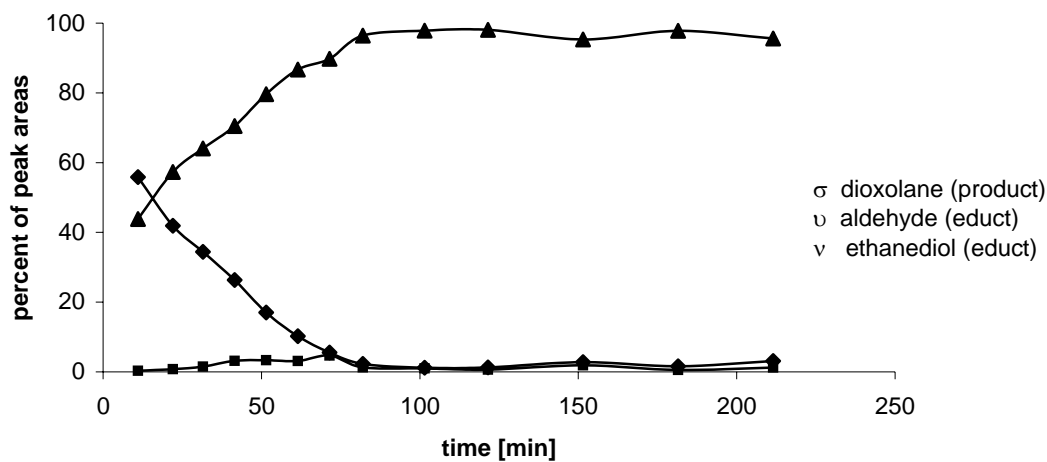
GC conditions:

column: Stabilwax-DA, L=30 m, d=0.32 mm, film=0.25  $\mu$ m (Restek)  
 inlet: injector 250 °C, split injection, injected volume 0.1  $\mu$ L  
 carrier gas: H<sub>2</sub>, precolumn pressure 150 kPa  
 oven: 100 °C (7.5 min), 4 °C/min 150 °C (0 min), 2 °C/min 170 °C (0 min), 1 °C/min 180 °C  
 detector: FID, 250 °C, H<sub>2</sub> 25.1 mL/min; synth. air 392 mL/min (275 kPa); make-up gas N<sub>2</sub>  
 integration: Integrator 4290 (Thermo Separation Products)

Percent concentration was calculated from peak areas

Retention time (min)	substance
3.87	ethanediol (educt)
23.5	3-nitrobenzaldehyde (educt)
34.0	1,3-dioxolane (product)

### Percent of peak areas of the reaction partners dependant on time

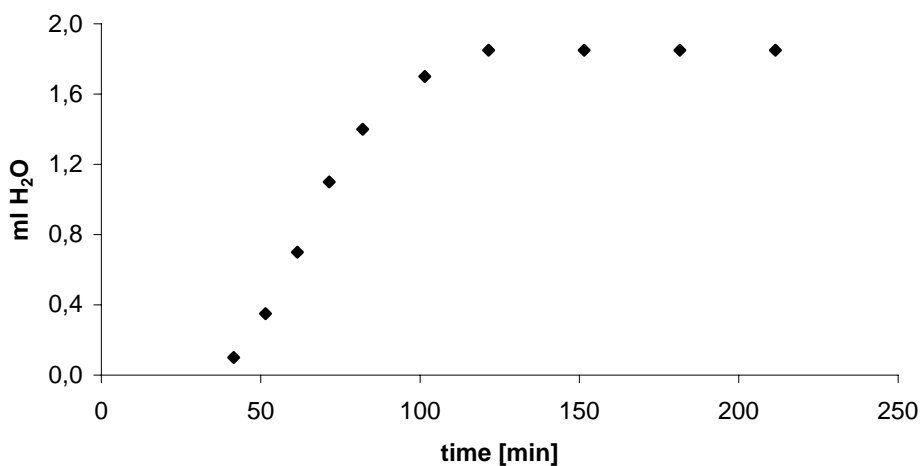


Batch scale: 100 mmol

The combination of the reaction components is defined as point 0 on the time scale.

The concentration curves of the reaction partners show that the ethanediol is only sparingly soluble in the solvent cyclohexane. Only with increasing temperature after 40 minutes is an increase in concentration in the solution evident.

### Timeframe of the water separation with same reaction scale



After 40 minutes the reaction solution is heated to reflux and the water separation starts.

## GC of the products

Sample preparation:

80 mg substance was solved in 0.5 mL *tert*-butyl methyl ether

GC conditions:

column: Zebron ZB-1, L=15 m, d=0.25 mm, film=0.25  $\mu$ m (Phenomenex)

inlet injector 250 °C, split injection, injected volume 0.15  $\mu$ L

carrier gas: He, precolumn pressure 101 kPa

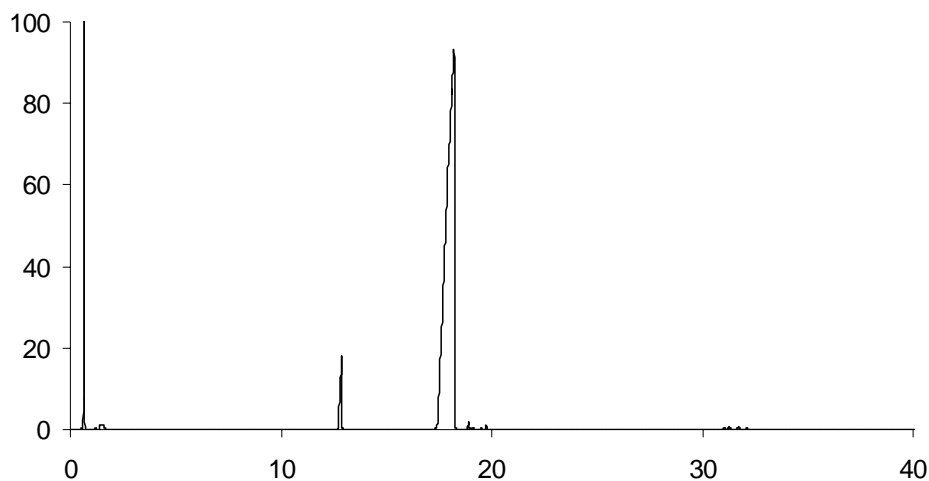
oven: 85 °C (0 min), 8 °C/min 250 °C (10 min)

detector: FID, 250 °C, H<sub>2</sub> 33.9 mL/min; synth air 322 mL/min; make-up gas N<sub>2</sub>, 15.0 mL/min (59 kPa)

integration: integrator 4290 (Thermo Separation Products)

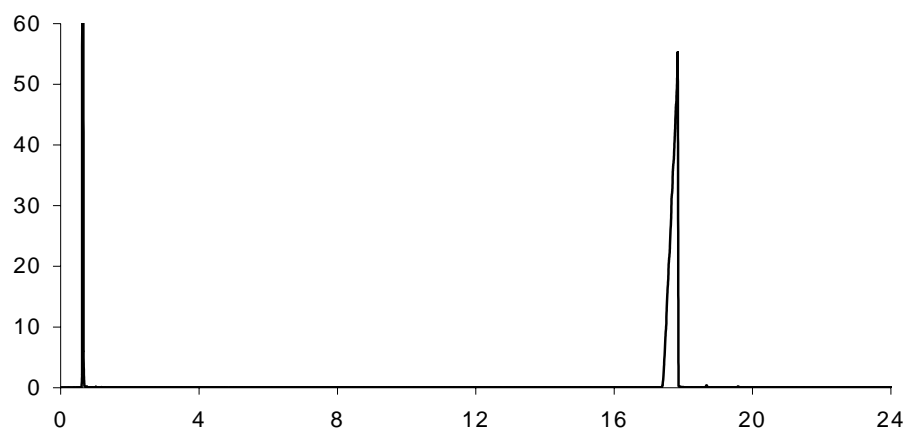
Percent concentration was calculated from peak areas

## GC of the crude product



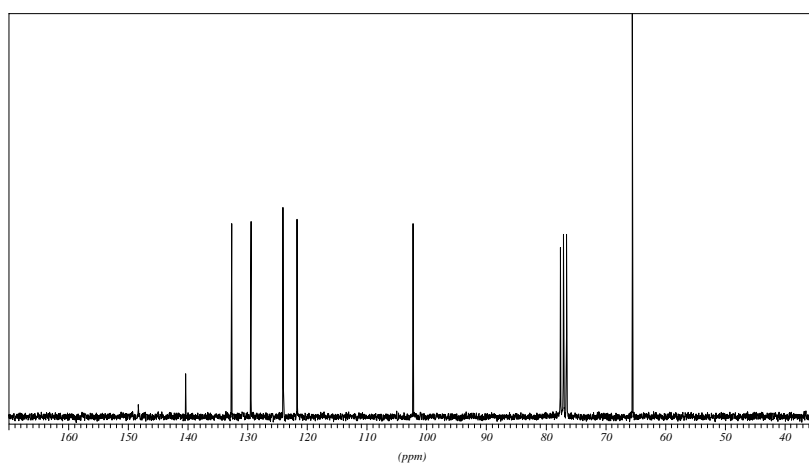
Retention time (min)	Substance	Peak area %
12.9	educt (3-nitrobenzaldehyde)	4.0
18.2	product (1,3-dioxolane)	94.7
others	not identified	1.3



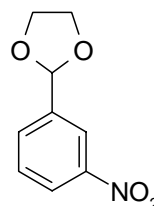
**GC of the product (not recrystallized)**

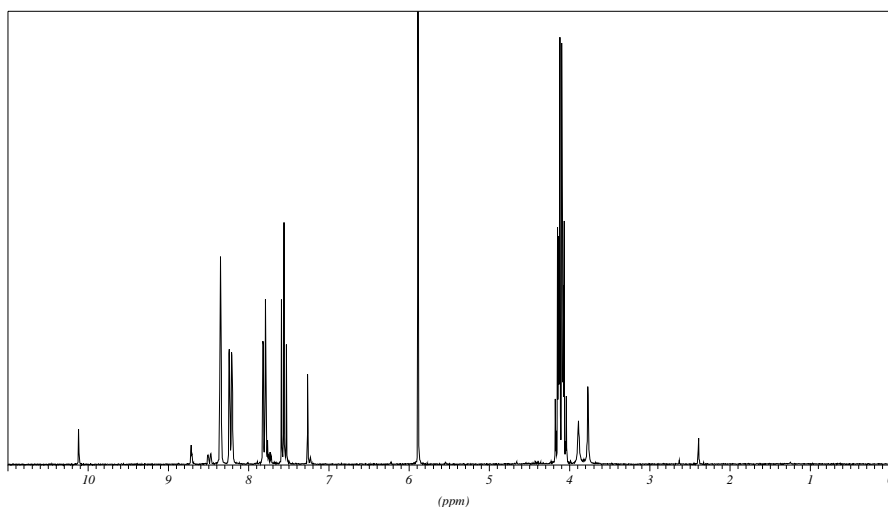
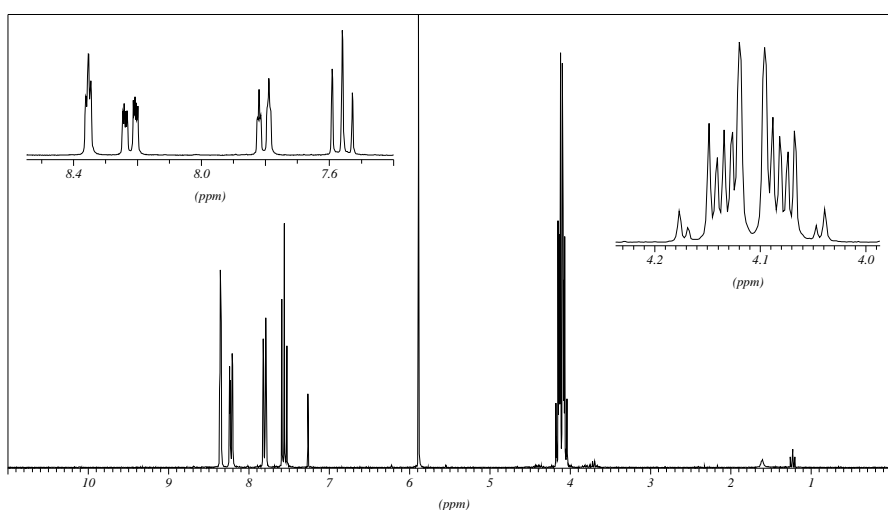
Retention time (min)	Substance	Peak area %
12.9	educt (3-nitrobenzaldehyde)	0.01
18.2	product (1,3-dioxolane)	99.6
others	not identified	0.3

The GC of the recrystallized product only shows traces (< 0.1%) of contamination.

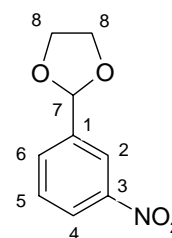
**<sup>13</sup>C NMR spectrum of the pure product (250 MHz, CDCl<sub>3</sub>)**

$\delta$ (ppm)	Assignment
65.5	- O - CH <sub>2</sub> - CH <sub>2</sub> - O -
102.3	- O - CH - O -
121.7	CH arene
124.0	CH arene
129.4	CH arene
132.7	CH arene
140.4	C - CH(dioxolane) arene
148.3	C - NO <sub>2</sub> arene
76.5-77.5	solvent



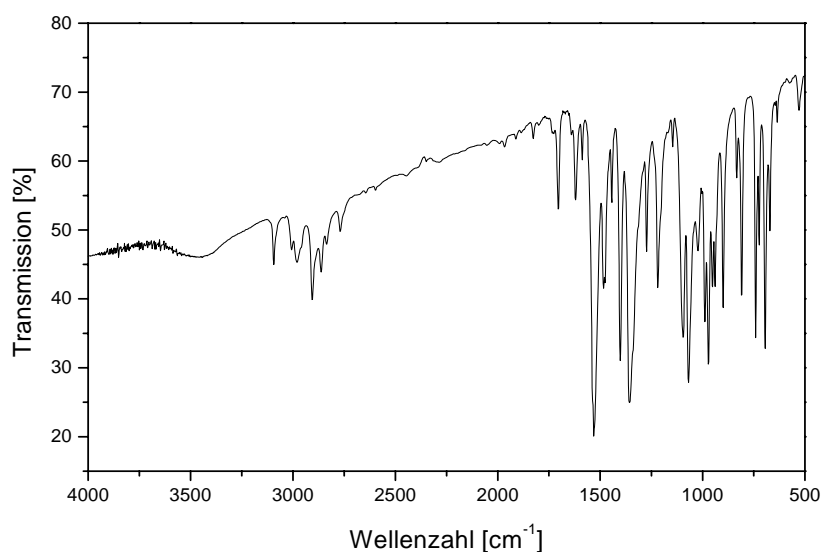
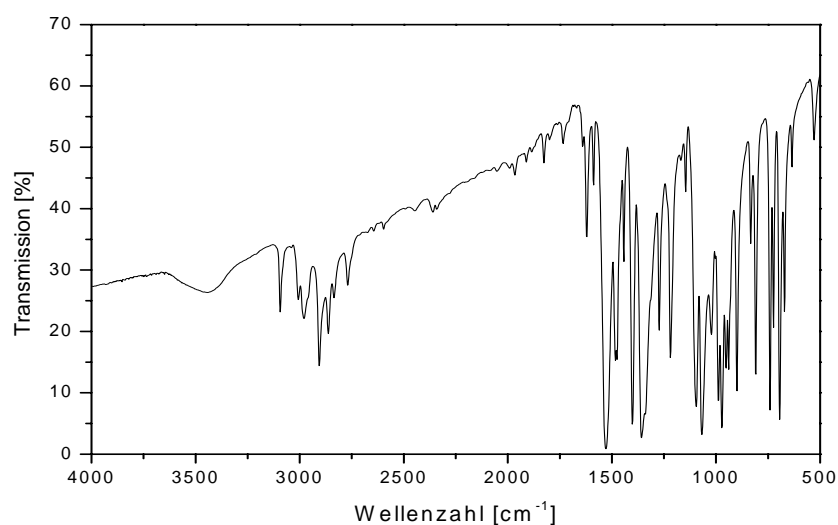
**$^1\text{H}$  NMR spectrum of the crude product (250 MHz,  $\text{CDCl}_3$ )** **$^1\text{H}$  NMR spectrum of the pure product (250 MHz,  $\text{CDCl}_3$ )**

$\delta$ (ppm)	Multiplicity	Number of H	Assignment
8.37 - 8.35	m	1	2-H
8.25 - 8.20	m	1	4-H
7.83 - 7.79	m	1	6-H
7.60 - 7.54	m	1	5-H
5.90	s	1	7-H
4.18 - 4.05	m	4	8-H
7.26			solvent



The weak signals at 1.23, 1.61 and 3.7 ppm originate from the ethanol of the recrystallization.

In the  $^1\text{H}$  NMR spectrum of the crude product one can see the resonance of the aldehyde proton of the starting material at 10.15 ppm.

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

( $\text{cm}^{-1}$ )	Assignment
3093	C – H – valence, arene
2978, 2905, 2862	C – H – valence, alkane
2769	C – H – valence, O – CH – O
1690 (only in crude product)	C = O – valence, aldehyde
1621, 1588	C = C – valence, arene
1532, 1359	N = O – valence, asymm. and symm.

In the IR spectrum of the crude product one can see the C=O band at  $1690\text{ cm}^{-1}$  of the still present starting material 3-nitrobenzaldehyde.

**Elemental analysis of the products before and after recrystallization**

	<b>% C</b>	<b>% H</b>	<b>% N</b>
calculated	55.39	4.65	7.18
found (before recrystallization)	55.54	4.38	7.16
	55.47	4.37	7.07
found (after recrystallization)	55.45	4.38	7.09
	55.61	4.40	7.17