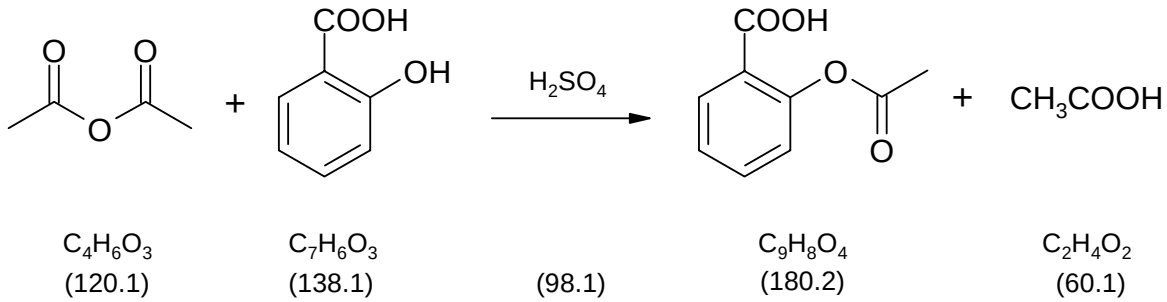
5012 Synthesis of acetylsalicylic acid (aspirin) from salicylic acid and acetic anhydride



$C_4H_6O_3$	$C_7H_6O_3$		$C_9H_8O_4$	$C_2H_4O_2$
(120.1)	(138.1)	(98.1)	(180.2)	(60.1)

Classification

Reaction types and substance classes

reaction of the carbonyl group in carboxylic acid derivatives, esterification
carboxylic acid anhydride, carboxylic acid ester, carboxylic acid, phenol, aromatics, acid catalyst

Work methods

microwave-assisted reaction, stirring with magnetic stir bar, heating under reflux, filtering, extracting, shaking out, recrystallizing

Instruction (batch scale 100 mmol)

Equipment

Microwave system ETHOS 1600, glass tube (40 cm, NS 29), 100 mL two-neck flask, magnetic stirrer, magnetic stir bar, intensive cooler, glass frit (diameter 6 cm), suction flask, desiccator

Substances

salicylic acid (mp 157-159 °C)	13.8 g (100 mmol)
acetic anhydride (bp 138-140.5 °C)	12.8 g (11.9 mL, 125 mmol)
conc. sulphuric acid (96%)	3 drops
sodium hydroxide	5 g
ethanol for recrystallizing	about 30 mL
aqueous iron(III) chloride solution (0.1 M)	a few mL

Reaction

The reaction apparatus consists of a 100 mL two-neck flask with magnetic stir bar, temperature sensor and intensive cooler. A mixture of 13.8 g (100 mmol) salicylic acid and 12.8 g (11.9 mL, 125 mmol) acetic anhydride is filled in the reaction flask and three drops of conc. sulphuric acid are added. The apparatus is installed by means of a glass tube in the

microwave system (see "Technical Instructions. Standard refluxing apparatus for microwave system"). The reaction mixture is heated under stirring for 90 seconds with 900 W to 140 °C. During the following cooling down the clear yellowish solution solidifies to a compact white crystalline mass.

Work up

After cooling down to room temperature, the solid is chopped in the flask and stirred for 30 minutes with 50 mL water. Then the solid is sucked off over a glass frit. The filter residue is washed on the frit three times with 30 mL water each, thereby the washing water runs through without vacuum, finally, it is thoroughly sucked off. The filtrate is disposed.

The crude product on the frit is analyzed with a 0.1 M iron(III) chloride solution for possibly contained salicylic acid (see analytics). If the test result is negative, the product is dried in the desiccator over granulated sodium hydroxide under reduced pressure until mass constancy. During the drying procedure also still adherent acetic acid is removed.
Yield: 16.0 g (88.8 mmol, 89%); mp 136 °C

For further purification, i.e. if the product still contains salicyl acid, it is recrystallized from ethanol/water: The crude product is dissolved under heating in about 30 mL ethanol, then about 60 mL hot water are added through the reflux condenser. The mixture is slowly cooled down and the flask is put in an ice bath to complete the crystallization. The product is sucked off and dried.
Yield: 14.6 g (81.0 mmol, 81%); mp 136 °C

Comments

Without addition of sulphuric acid the yield of the crude product amounted to about 83%, still containing bigger volumes of salicylic acid. After recrystallization the yield was below 70%.

If the humid product is pre-dried on a filter paper under the hood, considerably less drying agent is needed in the desiccator.

Waste management

Waste disposal

Waste	Disposal
aqueous filtrate	solvent water mixtures, halogen free
mother liquor from recrystallization	solvent water mixtures, halogen free

Time

About 1 hour without recrystallization

Break

Before work up

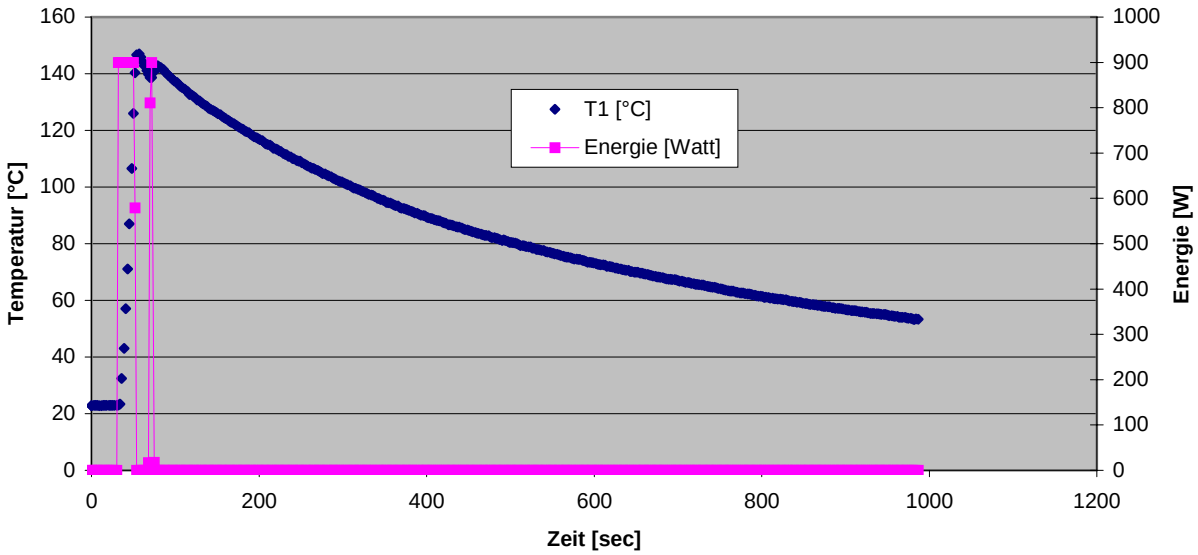
Degree of difficulty

Easy

Analytics

Temperature-time-dependence of the reaction steps in the microwave field

Synthesis of the acetylsalicylic acid

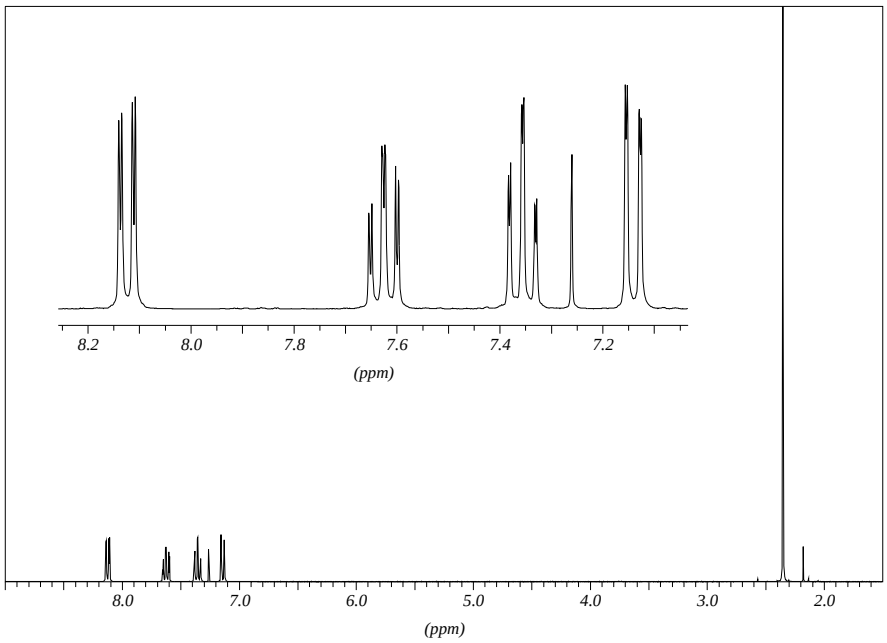


Iron(III) chloride test

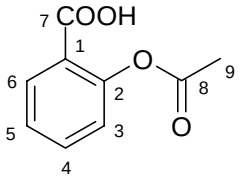
About 10 mg of the substance are dissolved in about 5 mL ethanol and 1 to 2 drops of a 0.1 M aqueous iron(III) chloride solution are added. An intensive violet colour of the solution shows the presence of salicylic acid.

Gas chromatography is not applicable as analysis method, since both salicylic acid as well as the product decarboxylate on the GC column.

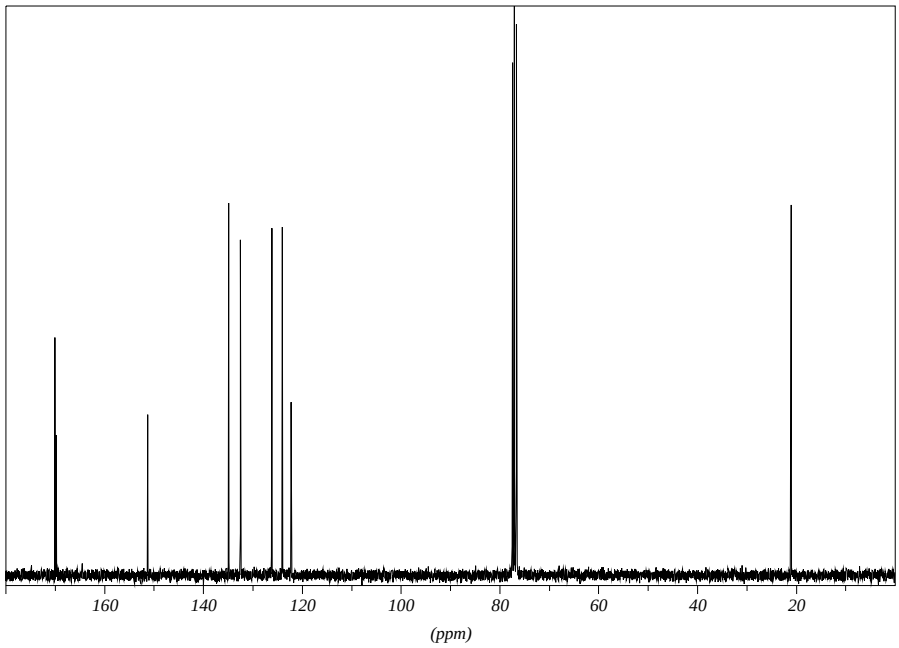
^{1}H NMR spectrum of the product (300 MHz, $CDCl_3$)



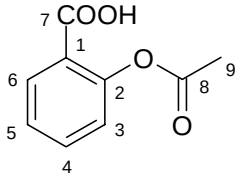
δ (ppm)	Multiplicity	Number of H	Assignment
8.12	dd	1	6-H
7.62	dt	1	4-H
7.36	dt	1	5-H
7.15	dd	1	3-H
2.35	s	3	CH_3
7.26			solvent



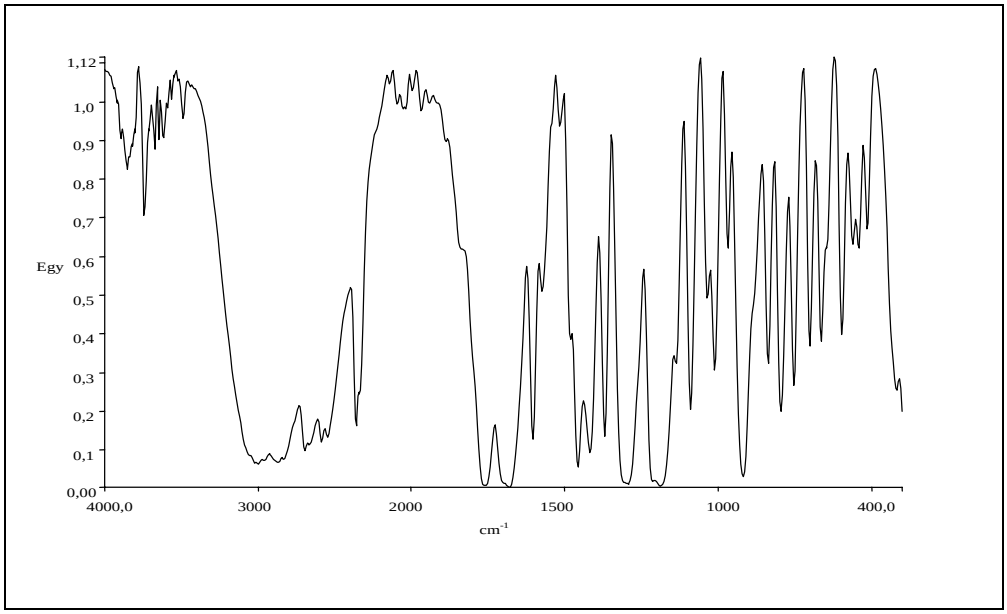
^{13}C NMR spectrum of the product (300 MHz, $CDCl_3$)



δ (ppm)	Assignment
170.06	C-7
169.78	C-8
151.25	C-2
134.90	C-4
132.52	C-6
126.18	C-5
124.01	C-3
122.24	C-1
21.02	CH_3
76.5-77.5	solvent



IR spectrum of the product (KBr)



(cm^{-1})	**Assignment**
3300 - 2500	O-H-valence, carboxylic acid, superimposed by C-H-valence
1760	C=O-valence, ester
1700	C=O-valence, carboxylic acid
1600, 1575	C=C-valence, arene