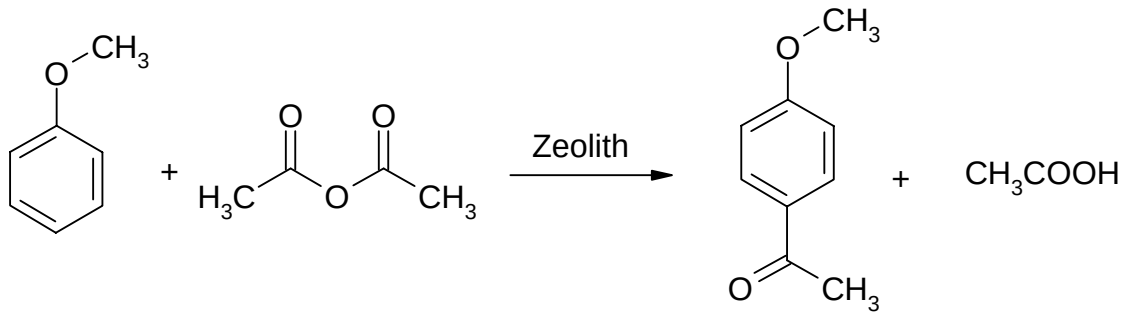
4010 Synthesis of *p*-methoxyacetophenone from anisole



C_7H_8O	$C_4H_6O_3$	$C_9H_{10}O_2$	$C_2H_4O_2$
(108.1)	(102.1)	(150.2)	(60.1)

Classification

Reaction types and substance classes

electrophilic substitution of aromatics, Friedel-Crafts acylation, reaction of the carbonyl group in carboxylic acid derivatives

aromatics, carboxylic acid anhydride, acid catalyst

Work methods

heating under reflux, stirring with magnetic stir bar, filtering, evaporating with rotary evaporator, distilling under reduced pressure, heating with oil bath

Instruction (batch scale 100 mmol)

Equipment

50 mL round-bottom flask, reflux condenser, Buechner funnel (Ø = 6.0 cm), suction flask, heatable magnetic stirrer with magnetic stir bar, rotary evaporator, distillation apparatus, oil bath

Substances

anisole (bp 156 °C)	10.8 g (10.9 mL, 100 mmol)
acetic anhydride (bp. 140 °C)	15.3 g (14.2 mL, 150 mmol)
Zeolith H-BEA 25 (Süd-Chemie)	2.88 g
ethanol (bp 78 °C)	20 mL

Reaction

10.8 g (10.9 mL, 100 mmol) anisole, 15.3 g (14.2 mL, 150 mmol) acetic anhydride and 2.88 g Zeolith H-BEA 25 are placed into a 50 mL round-bottom flask containing a magnetic stir bar and fitted with a reflux condenser. The reaction mixture is heated with stirring for 6 hours to 150 °C.

Work up

The catalyst is filtered off using a Buechner funnel (Ø = 6.0 cm) and washed with 20 mL ethanol. The filtrate is concentrated on a rotary evaporator.
Crude yield: 16.2 g; GC-purity 78% (see analytics)

The crude product is fractionally distilled under vacuum at 12 hPa (oil bath temperature up to 165 °C). Yield:

Fraction 1: bp 45 °C (12 hPa) (educt)
Fraction 2: bp 138 °C (12 hPa) (product); 11.6 g (77.2 mmol, 77%), white solid, mp 36 °C; GC-purity > 99%

Comments

When an equimolar amount of anisole and acetic anhydride is used, a reaction time of at least 20 hours is needed. By using an excess of 1.5 equivalents acetic anhydride, the reaction time is reduced to 6 hours.

Waste management

Waste disposal

Waste	Disposal
fraction 1 from distillation	organic solvents, halogen free
distillation residues	dissolve in a small amount of acetone, then: organic solvents, halogen free
ethanol used for washing	organic solvents, halogen free
residues from catalyst	solid waste, free from mercury

Time

6 hours for the reaction, 3 hours for the distillation.

Break

After heating under reflux and after concentrating with the rotary evaporator.

Degree of difficulty

Easy

Instruction (batch scale 10 mmol)

Equipment

10 mL round-bottom flask, reflux condenser, Buechner funnel (Ø = 2.0 cm), suction flask, heatable magnetic stirrer with magnetic stir bar, rotary evaporator, kugelrohr distillation apparatus or microdistillatin apparatus, oil bath

Substances

anisole (bp 156 °C)	1.08 g (1.09 mL, 10.0 mmol)
acetic anhydride (bp. 140 °C)	1.53 g (1.42 mL, 15.0 mmol))
Zeolith H-BEA 25 (Süd-Chemie)	0.29 g
ethanol (bp 78 °C)	15 mL

Reaction

1.08 g (1.09 mL, 10.0 mmol) anisole, 1.53 g (1.42 mL, 15.0 mmol) acetic anhydride and 0.288 g Zeolith H-BEA 25 are placed into a 10 mL round-bottom flask containing a magnetic stir bar and fitted with a reflux condenser. The reaction mixture is heated with stirring for 6 hours to 150 °C.

Work up

The catalyst is filtered off using a Buechner funnel (Ø = 2.0 cm) and washed with 15 mL ethanol. The filtrate is concentrated on a rotary evaporator.
Crude yield: 1.35 g

The crude product is distilled in a kugelrohr distillation apparatus at 25 hPa (oil bath temperature up to 165 °C).
Yield: 1.11 g (7.39 mmol, 74%), white solid, mp 35.6-37.5 °C

Comments

When an equimolar amount of anisole and acetic anhydride is used, a reaction time of at least 20 hours is needed. By using an excess of 1.5 equivalents acetic anhydride, the reaction time is reduced to 6 hours.

Waste management

Waste disposal

Waste	Disposal
distillation residues	dissolve in a small amount of acetone, then: organic solvents, halogen free
ethanol used for washing	organic solvents, halogen free
residues from catalyst	solid waste, free from mercury

Time

6 hours for the reaction, 1.5 hours for the distillation.

Break

After heating under reflux and after concentrating with the rotary evaporator.

Degree of difficulty

Easy

Analytics

Reaction monitoring by GC

Sample preparation:

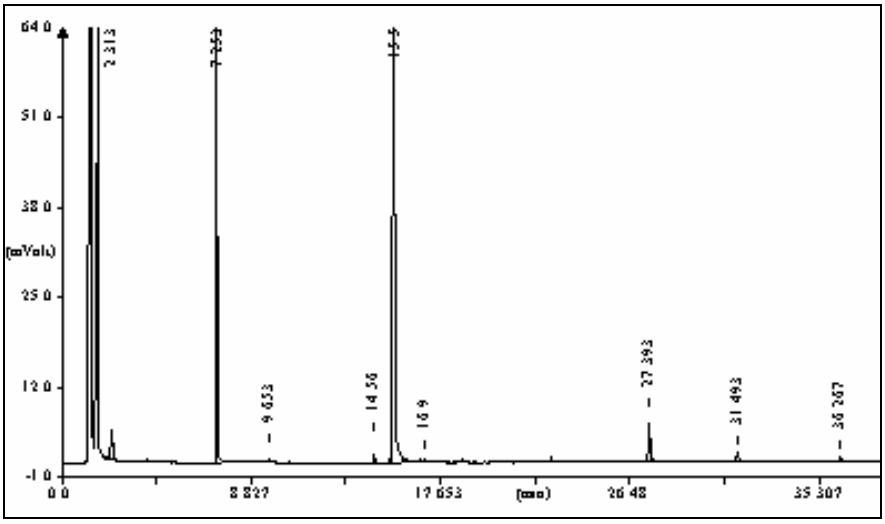
Using a Pasteur pipette, one drop of the reaction mixture is taken, diluted with 10 mL dichloromethane and filtered. From the filtrate, 0.2 µL are injected.

GC conditions:

column:	DB-1, L=28 m, d=0.32 mm, film=0.25 μm
inlet:	On-column injection, injected volume 0.2 μL
carrier gas:	H_2 (40 cm/s
oven:	40 °C (5 min), 10 °C/min 240 °C (30 min)
detector:	FID, 270 °C

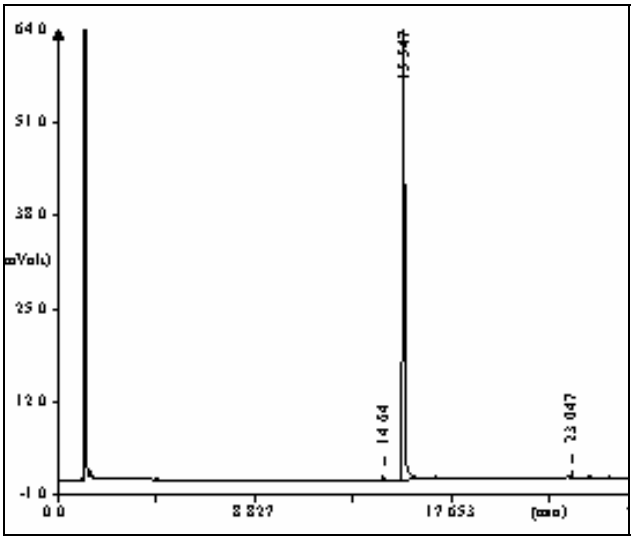
Percent concentration was calculated from peak areas

GC of the crude product



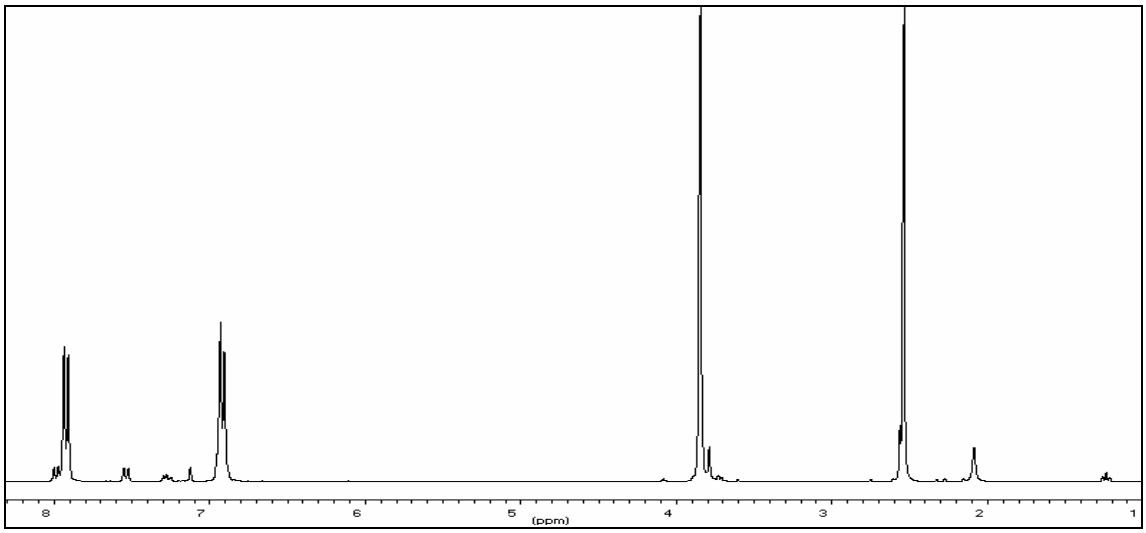
Retention time (min)	Substance	peak area %
2.31	educt (acetic anhydride)	5.8
7.25	educt (anisole)	14.4
15.50	product (*p*-methoxyacetophenone)	77.8
27.39	side product	0.96

GC of the pure product

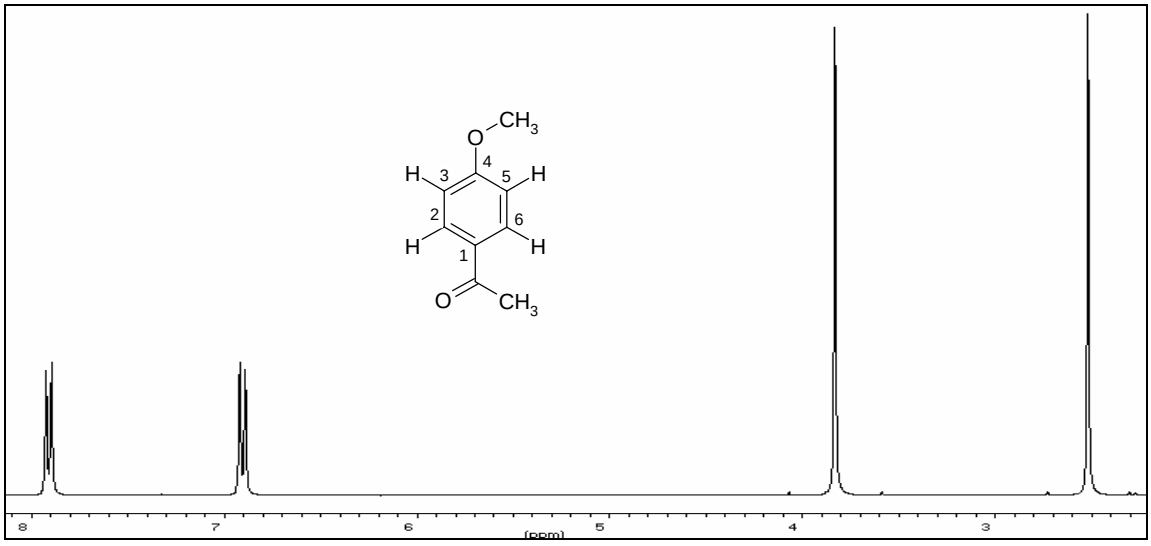


Retention time (min)	Substance	peak area %
15.55	product (*p*-methoxyacetophenone)	99.7

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

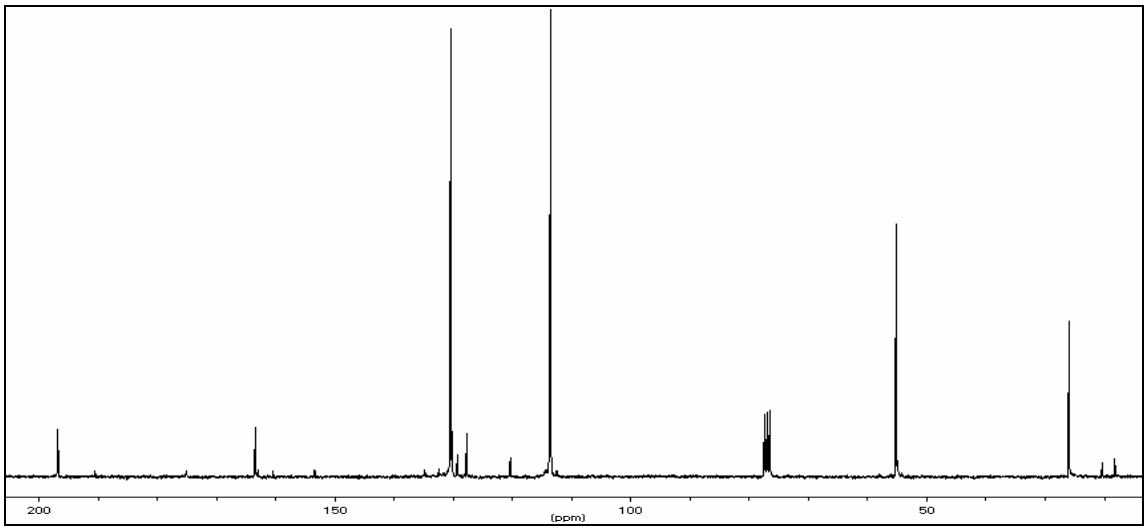


^{1}H NMR spectrum of the pure product (300 MHz, $CDCl_3$)

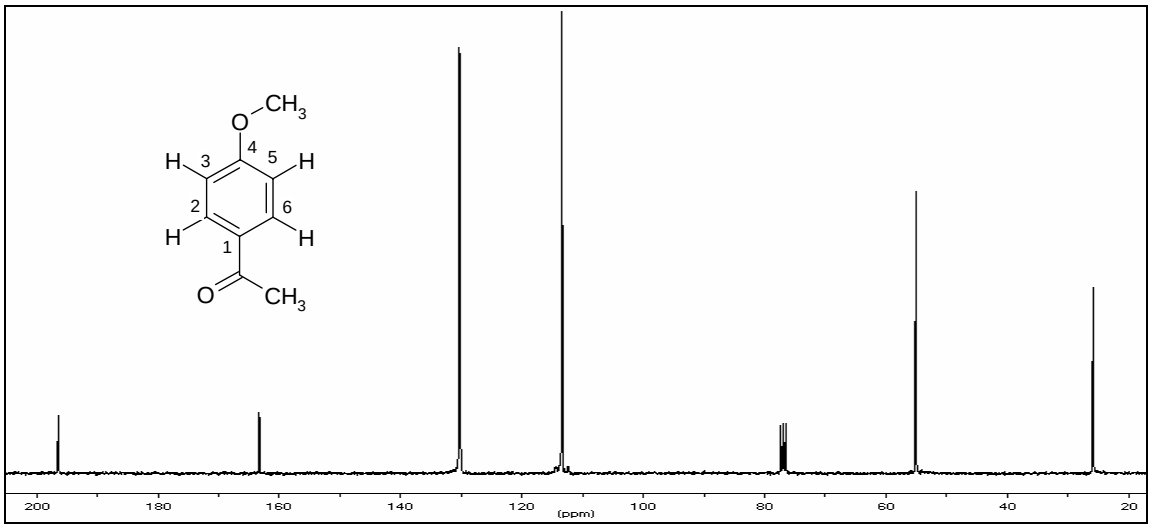


δ (ppm)	Multiplicity	Number of H	Assignment
2.54	s	3	-CO-CH_3
3.85	s	3	-O-CH_3
6.91	m (AA´)	2	3-H, 5-H
7.91	m (XX´)	2	2-H, 6-H

^{13}C NMR spectrum of the crude product (75.5 MHz, $CDCl_3$)

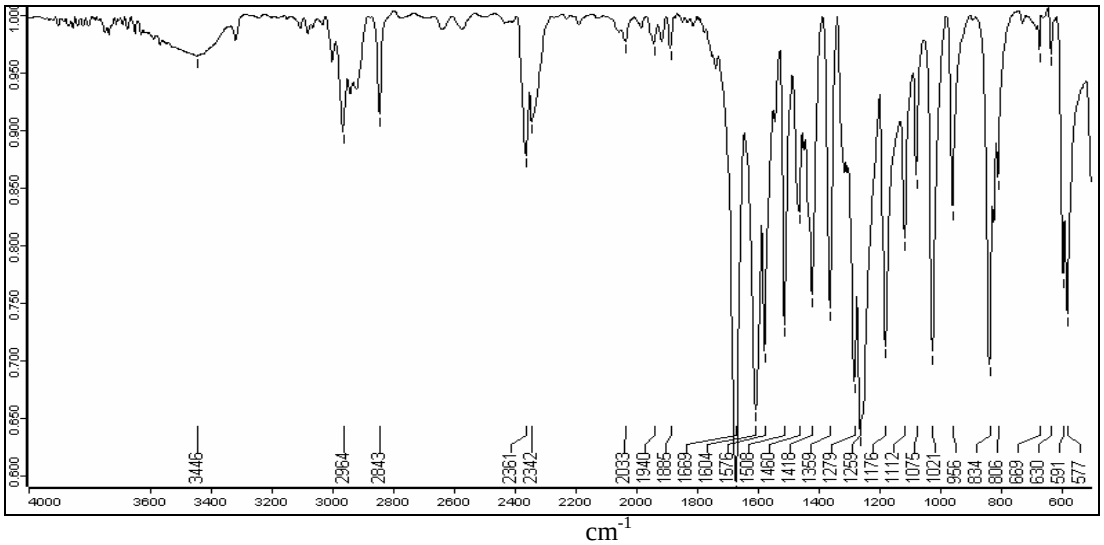


^{13}C NMR spectrum of the pure product (75.5 MHz, $CDCl_3$)



δ (ppm)	Assignment
196.34	-**C**O-CH_3
163.25	C-4
130.29	C-2, C-6
130.09	C-1
113.43	C-3, C-5
55.15	-O-**C**H_3
25.98	-CO-**C**H_3
76.5-77.57	solvent

IR spectrum of the pure product (Film)



(cm^{-1})	**Assignment**
3000	C-H-valence, arene
2964	C-H-valence, alkane
2843	C-H-valence, alkane, O-CH_3
1617	C=O-valence, ketone
1604, 1576, 1508	C=C-valence, arene