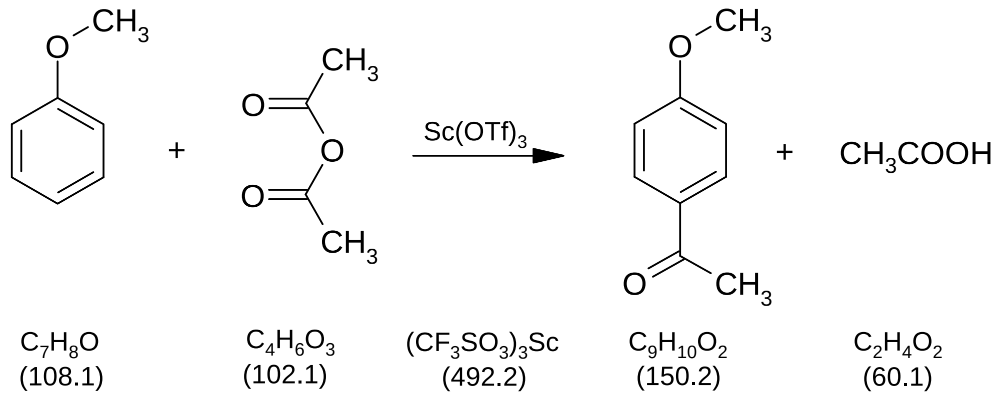
1035 Synthesis of p-methoxyacetophenone from anisole



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

working with protective gas, adding dropwise with an addition funnel, shaking out, extracting, filtering, distilling under reduced pressure, evaporating with rotary evaporator, stirring with magnetic stir bar, heating with oil bath

Instruction (batch scale 50 mmol)

Equipment

500 mL three-neck flask, internal thermometer, protective gas piping, electronic temperature control, reflux condenser, drying tube, addition funnel with pressure balance, heatable magnetic stirrer with magnetic stir bar, 500 mL separating funnel, microdistillation apparatus, rotary evaporator, vacuum pump, oil bath

Substances

anisole (bp 156 °C)	5.40 g (5.45 mL, 50.0 mmol)
acetic anhydride (bp 140 °C)	5.10 g (4.7 mL, 50.0 mmol)
scandium(III)-triflate	4.90 g (10.0 mmol)
nitromethane (bp 101 °C)	60 mL
tert-butyl methyl ether (bp 55 °C)	140 mL
magnesium sulfate for drying	about 3 g
sodium chloride	about 40 g (for 100 mL saturated aqueous solution)

Reaction

Drying of scandium(III) triflate: Heat 4.90 g (10.0 mmol) of $Sc(OTf)_3$ for 1 hour in an evacuated (approx. 1 hPa) 500 mL three-neck flask with nitrogen and vacuum inlet to 180 °C in an oil bath to remove all moisture. Inflate the flask with nitrogen.

After cooling to room temperature, the flask is equipped with reflux condenser with drying tube, pressure equalizing dropping funnel and internal thermometer while maintaining a nitrogen atmosphere. Charge the flask with 60 mL of nitromethane via the dropping funnel and stir for 10 minutes. Add, again using the dropping funnel, 5.40 g (5.45 mL, 50.0 mmol) of anisole and 5.10 g (4.7 mL, 50.0 mmol) of acetic anhydride. The reaction mixture is heated with stirring for 6 hours to 50 °C internal temperature.

Work up

After cooling to room temperature, add 150 mL of water and transfer the mixture into a separating funnel. The organic phase is separated and the aqueous phase extracted twice with 70 mL of tert-butyl methyl ether. Wash the combined organic phases with 100 mL of brine, and dry over magnesium sulfate. The magnesium sulfate is removed by filtration and the solvent removed at a rotary evaporator to yield a slightly yellow residue as crude product.
Yield of crude product: 7.81 g; purity according to GC 96%

The crude product is distilled in a microdistillation apparatus in vacuum.

Yield:
First fraction 0.49 g; bp up to 100 °C (0.6 hPa). GC shows 2% *ortho*-methoxyacetophenone beside *para*-methoxyacetophenone.
Second fraction 4.46 g (29.7 mmol, 59%); bp 110 °C (0.6 hPa); colourless liquid, which rapidly solidifies; purity according to GC 99%
Residue of distillation: 1.24 g of tar

Recovery of the catalyst

Concentrate the combined aqueous phases with the rotary evaporater as far as possible. The remaining crystalline residue is dried in vacuum (approx. 1 hPa) at 180 °C for 20 hours.
Yield of recovered scandium(III) triflate 3.50 g (70% of the amount originally used in the reaction). Fresh and recovered scandium catalysts give the same results in the reaction.

Comments

The condensate of the cryogenic trap of the vacuum pump is composed of nitromethane and anisole according to 1H NMR spectrum.

Waste management

Recycling

Scandium triflate is recovered.

Waste disposal

Waste	Disposal
evaporated solvent mixture	organic solvents, halogen free
distillation residue	organic solvents, containing halogen, containing heavy metals
magnesium sulfate	solid waste, free from mercury
evaporated water	sewage

Time

11 hours, without recovery of the scandium triflate

Break

Before work up and before distillation

Degree of difficulty

Medium

Analytics

Reaktion monitoring

TLC is not sensitive enough for reaction monitoring in this case. After 1.5 hours reaction time TLC shows complete anisole conversion, while GC analysis of the crude product detects anisole even after 4 hours of reaction time.

TLC

TLC conditions:

adsorbent:	Macherey and Nagel Polygram SilG/UV plates, 0.2 mm
elution solvent:	*n*-heptane/ethyl acetate 9:1

Dry the TLC after the first development and place it for a second development again into the eluent chamber to detect the side product *ortho*-methoxyacetophenone.

R_f	Substance
0.84	anisole
0.42	*para*-methoxyacetophenone
0.47	*ortho*-methoxyacetophenone

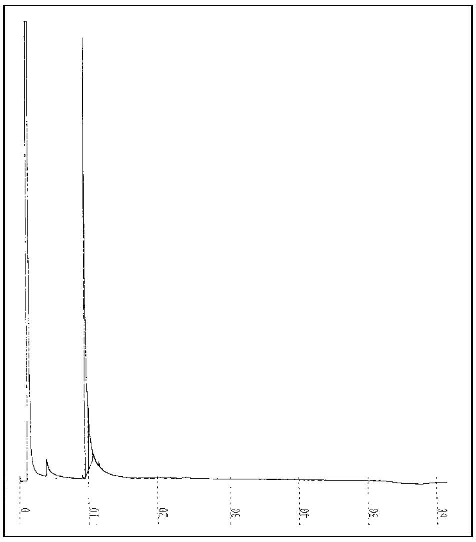
GC

GC conditions:

column:	5CB Low Blend/MS, L=20 m, d=0.32 mm, film=0.25 μm
inlet:	injector 210 °C, split injection, injected volume 0.1 μL
carrier gas:	H_2, precolumn pressure 50 kPa
oven:	60 °C (2 min), 10 °C/min, isotherm 240 °C (30 min)
detector:	FID, 310
integration:	Shimadzu

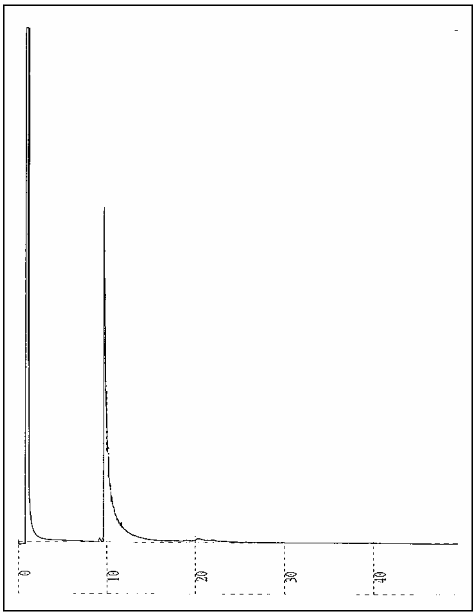
Percent concentration was calculated from peak areas

GC of the crude product



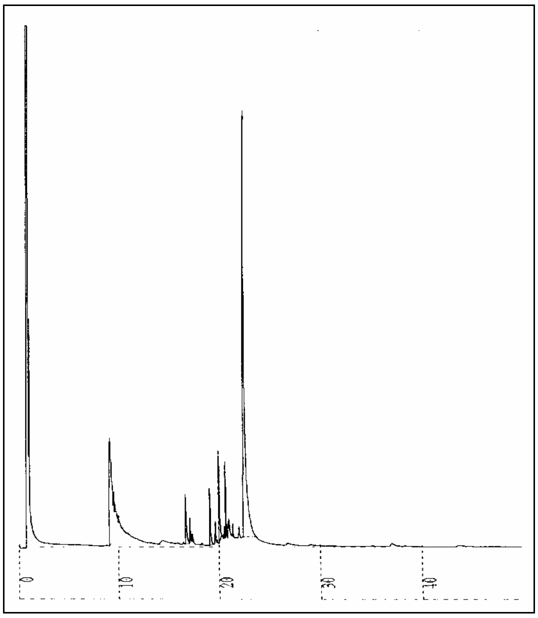
Retention time (min)	Substance	Peak area %
3.85	anisole	4
9.54	*p*-methoxyacetophenone	96

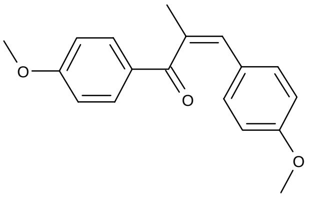
GC of the pure product



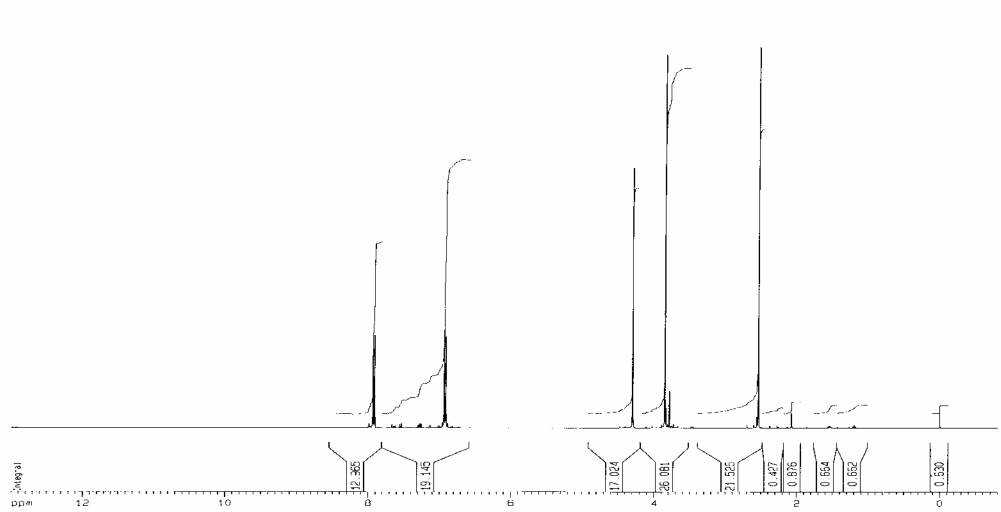
Retention time (min)	Substance	Peak area %
9.7	*p*-methoxyacetophenone	99

GC of the residue of distillation

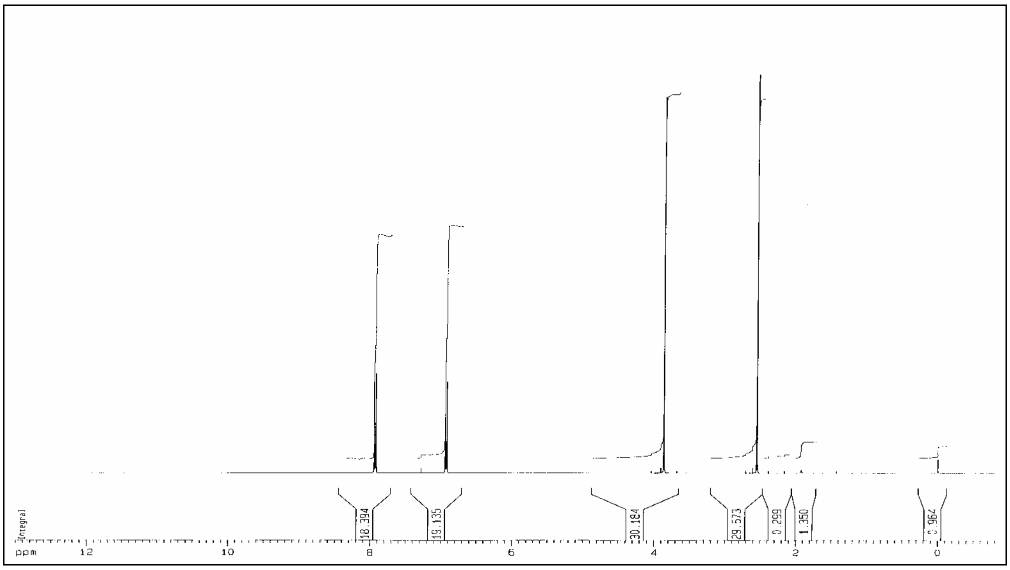


Retention time (min)	Substance	Peak area %
9.5	*p*-methoxyacetophenone	14.8
19.9 and 22.5	Substances with mass 282, a possibility for the structure: 	16.9 and 61.8

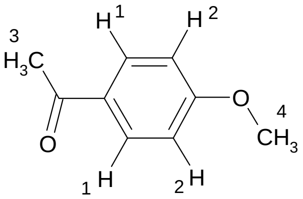
^{1}H NMR spectrum of the crude product (400 MHz, $CDCl_3$)



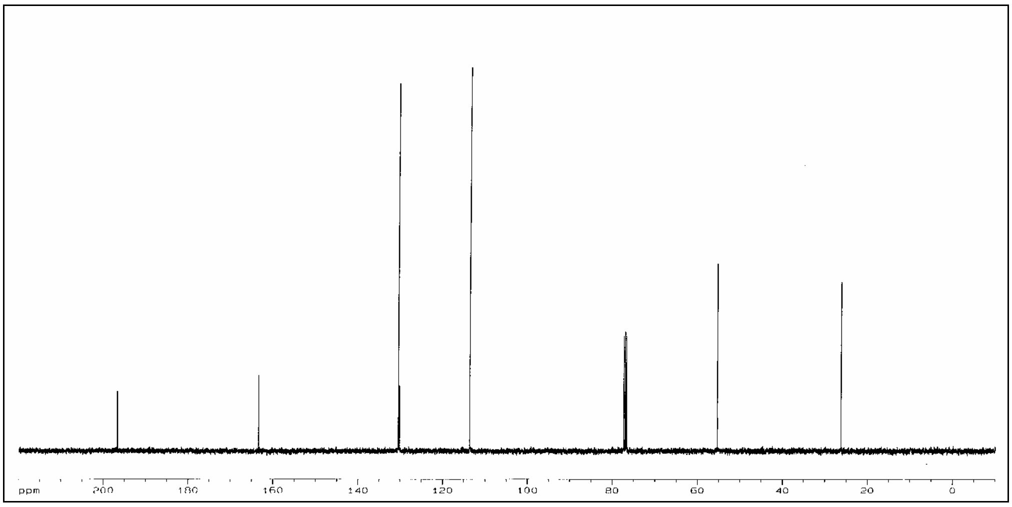
^{1}H NMR spectrum of the pure product (400 MHz, $CDCl_3$)



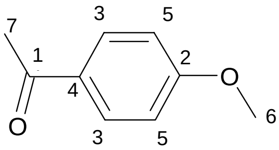
δ (ppm)	Multiplicity	Number of H	Assignment
2.55	s	3	3-H
3.86	s	3	4-H
6.91 – 6.95	m (AA´)	2	2-H
7.91 – 7.95	m (XX´)	2	1-H
4.3 (crude product only)	s		nitromethane



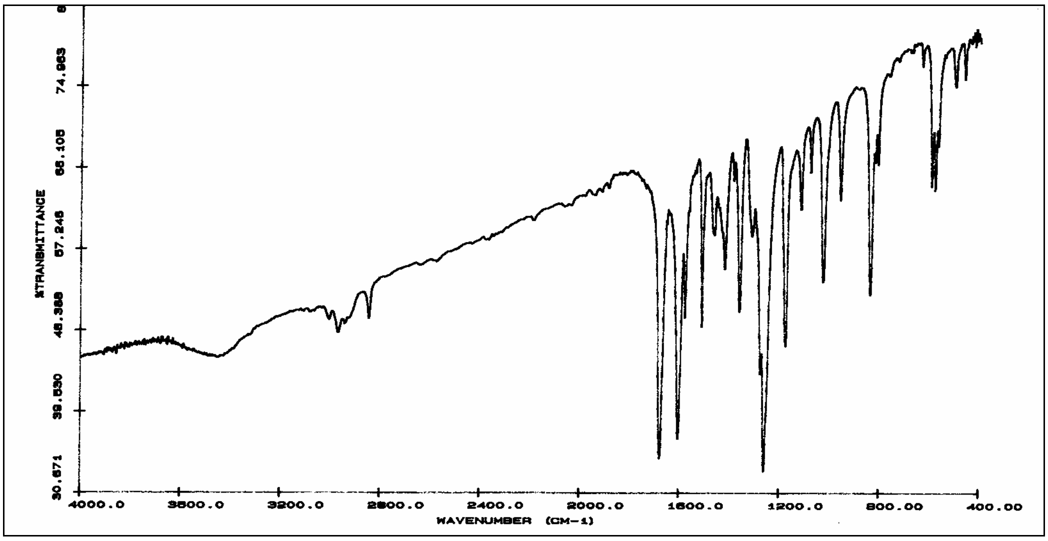
^{13}C NMR spectrum of the pure product (100 MHz, $CDCl_3$)



δ (ppm)	Assignment
26.2	C-7
55.4	C-6
113.6	C-5
130.2	C-4
130.5	C-3
163.4	C-2
196.7	C-1



IR spectrum of the pure product (KBr)



(cm^{-1})	**Assignment**
3000	C – H – valence, arene
2960	C – H – valence, alkane
2840	C – H – valence, alkane, O-CH_3
1675	C = O – valence, ketone
1602, 1580, 1500	C = C – valence, arene