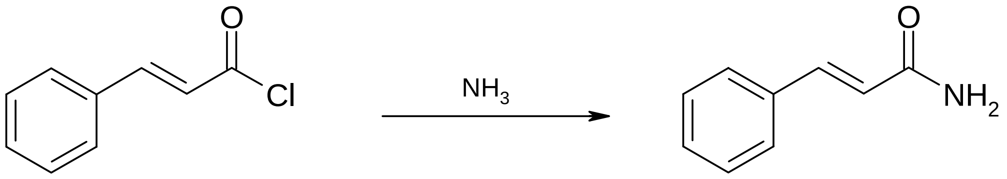
2017 Reaction of cinnamic acid chloride with ammonia to cinnamic acid amide



C_9H_7ClO (166.6) (17.0) C_9H_9NO (147.2)

Classification

Reaction types and substance classes

reaction of the carbonyl group in carboxylic acid derivatives
carboxylic acid amide, carboxylic acid chloride

Work methods

stirring with magnetic stir bar, adding dropwise with an addition funnel, shaking out, extracting, evaporating with rotary evaporator, recrystallizing, filtering, use of an ice cooling bath

Instruction (batch scale 100 mmol)

Equipment

250 mL three-neck flask, reflux condenser, addition funnel without pressure balance, magnetic stirrer, magnetic stir bar, 500 mL separating funnel, rotary evaporator, ice bath, vacuum pump

Substances

trans-cinnamic acid chloride (mp 32-35°C, bp 251-258 °C; distilled; product from experiment 2013)	16.6 g (100 mmol)
aqueous conc. ammonia solution (25%)	80 mL (70 g, 1.0 mol)
tert-butyl methyl ether (bp 55 °C)	80 mL
acetic acid ethyl ester (bp 77 °C)	140 mL
sodium sulfate for drying	about 5 g

Reaction

80 mL aqueous conc. ammonia solution are filled in a 250 mL three-neck flask with reflux condenser, magnetic stir bar and addition funnel without pressure balance. The reaction flask is cooled in an ice bath. A solution of 16.6 g (100 mmol) *trans*-cinnamic acid chloride in 80 mL *tert*-butyl methyl ether is transferred into the addition funnel and added under stirring (within about 30 minutes) thereby avoiding a too strong reaction. Afterwards stirring is

continued for 30 min at room temperature. A fine white solid precipitates, which is not isolated.

Work up

The content of the reaction flask is transferred into a 500 mL separating funnel. The flask is rinsed initially with about 50 mL water and then with 50 mL acetic acid ethyl ester. These washing solutions are also filled into the separating funnel. The funnel is strongly shaken, then the phases are separated The aqueous phase is shaken out three times with 30 mL acetic acid ethyl ester each and stored.

The combined organic phases are dried over sodium sulfate, the drying agent is filtered off and the solvent is evaporated at the rotary evaporator. Cinnamic acid amide remains as a white solid, which is dried under high vacuum until it is constant in weight.
Yield: 12.0 g (81.5 mmol, 82%); mp 146-148 °C; HPLC purity over 99%

The product can be recrystallized from water, afterwards it has to be dried thoroughly under high vacuum, until all water has been removed (constant weight).
Yield: 10.8 g (73.4 mmol, 73%); mp 147-148 °C. Spectra and HPLC do not differ from the not recrystallized product.

The aqueous phase can be acidified, then shaken out twice with 50 mL acetic acid ethyl ester each. After drying of the organic phase with sodium sulfate and evaporating of the solvent, at the rotary evaporator about 200 mg of a white solid remain as residue. It consists to 80% of cinnamic acid amide and to 20% of cinnamic acid (see analytics). The aqueous phase contains no substances which can be detected with the described HPLC-conditions. After evaporation of the water at the rotary evaporator a solid residue remains, mainly consisting of ammonium chloride.

Comments

If the raw and undistilled cinnamic acid chloride is used for the reaction, (13.5 g, see experiment 2013), cinnamic acid amide is isolated (without recrystallization) with a yield of 9.65 g (65.6 mmol, 66% with reference to the used cinnamic acid (14.8 g, 100 mmol)).

When adding the cinnamic acid chloride to the conc. ammonia solution, it is not allowed to use an addition funnel with pressure balance since the ammonia vapours otherwise rise up into the acid chloride solution, there reacting to amide, which precipitates and congests the addition funnel. The acid chloride solution can also be added through a septum by using a syringe

Waste management

Waste disposal

Waste	Disposal
distilled solvent mixture	organic solvents, halogen free
aqueous phase	solvent water mixtures, containing halogen
sodium sulfate	solid waste, free from mercury
aqueous mother liquor	solvent water mixtures, halogen free

Time
About 2 hours without recrystallization

Break
Before and after shaking out

Degree of difficulty
Easy

Instruction (batch scale 10 mmol)

Equipment

100 mL three-neck flask, reflux condenser, addition funnel without pressure balance, magnetic stirrer, magnetic stir bar, 100 mL separating funnel, rotary evaporator, ice bath, vacuum pump

Substances

trans-cinnamic acid chloride (mp 32-35°C, bp 251-258 °C; distilled; product from experiment 2013)	1.66 g (10.0 mmol)
aqueous conc. ammonia solution (25%)	10 mL (8.7 g, 125 mmol)
tert-butyl methyl ether (bp 55 °C)	10 mL
acetic acid ethyl ester (bp 77 °C)	40 mL
sodiumsulfate for drying	about 1 g

Reaction

10 mL aqueous conc. ammonia solution are filled in a 100 mL three-neck flask with reflux condenser, magnetic stir bar and addition funnel without pressure balance. The reaction flask is cooled in an ice bath. A solution of 1.66 g (10.0 mmol) *trans*-cinnamic acid chloride in 10 mL *tert*-butyl methyl ether is transferred into the addition funnel and added under stirring (within about 15 minutes) thereby avoiding a too strong reaction. Afterwards stirring is continued for 30 min at room temperature. A fine white solid precipitates, which is not isolated.

Work up

The content of the reaction flask is transferred into a 100 mL separating funnel. The flask is rinsed initially with about 10 mL water and then with 10 mL acetic acid ethyl ester. These washing solutions are also filled into the separating funnel. The funnel is strongly shaken, then the phases are separated. The aqueous phase is shaken out three times with 10 mL acetic acid ethyl ester each and stored.

The combined organic phases are dried over sodium sulfate, the drying agent is filtered off and the solvent is evaporated at the rotary evaporator. Cinnamic acid amide remains as a white solid, which is dried under high vacuum until it is constant in weight.
Yield: 1.15 g (7.81 mmol, 78%); mp 146-148 °C; HPLC purity over 99%

The product can be recrystallized from water, afterwards it has to be dried thoroughly under high vacuum, until all water has been removed (constant weight).
Yield: 900 mg (6.12 mmol, 61%); mp 147-148 °C. Spectra and HPLC do not differ from the not recrystallized product.

Comments

If the raw and undistilled cinnamic acid chloride is used for the reaction, (1.4 g, see experiment 2013), cinnamic acid amide is isolated (without recrystallization) with a yield of 1.05 g (7.14 mmol, 71% with reference to the used cinnamic acid (1.4 g, 100 mmol)).

When adding the cinnamic acid chloride to the conc. ammonia solution, it is not allowed to use an addition funnel with pressure balance since the ammonia vapours otherwise rise up into the acid chloride solution, there reacting to amide, which precipitates and congests the addition funnel. The acid chloride solution can also be added through a septum by using a syringe

Waste management

Waste disposal

Waste	Disposal
distilled solvent mixture	organic solvents, halogen free
aqueous phase	solvent water mixtures, containing halogen
sodium sulfate	solid waste, free from mercury
aqueous mother liquor	solvent water mixtures, halogen free

Time

About 1,5 hours without recrystallization

Break

Before and after shaking out

Degree of difficulty

Easy

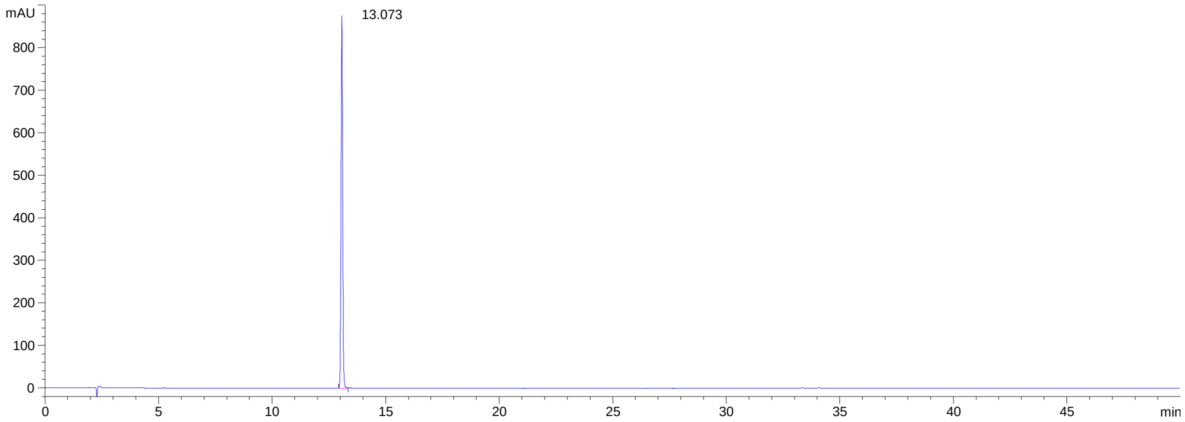
Analytics

HPLC

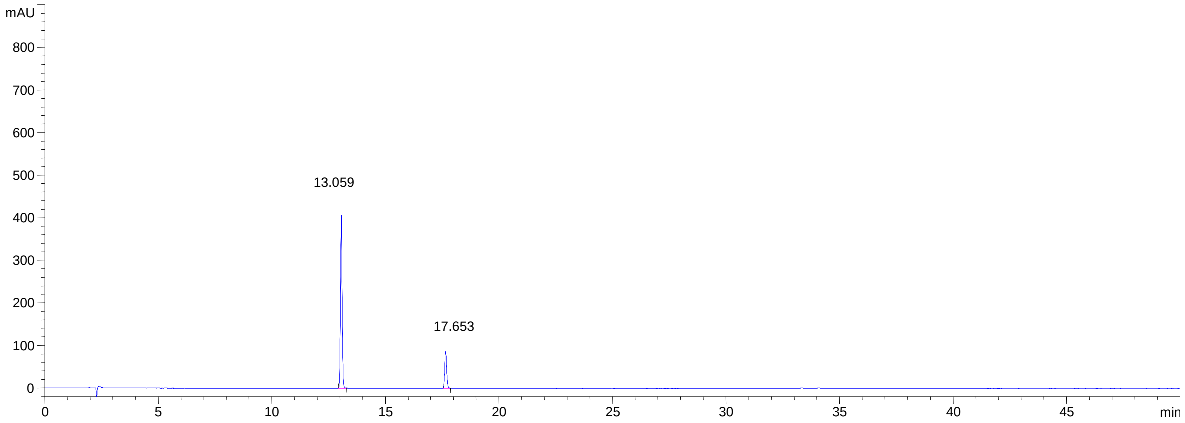
Sample preparation:	0.1 mg substance are dissolved in 1 mL acetonitrile.
HPLC conditions:	
column:	Phenomenex Luna C18; size 3 µm, length 150 mm, internal diameter 4.6 mm
column temperature	25 °C
injection volume:	5.0 µL
gradient:	0 min 5% acetonitrile + 95% water (+ 0.0059% trifluoroacetic acid)
	40 min 95% acetonitrile + 5% water (+ 0.0059% trifluoroacetic acid)
	50 min 95% acetonitrile + 5% water (+ 0.0059% trifluoroacetic acid)
flow:	1.0 mL/min
wavelength:	220 nm

Percent concentration was calculated from peak areas.

HPLC I of the product before recrystallization

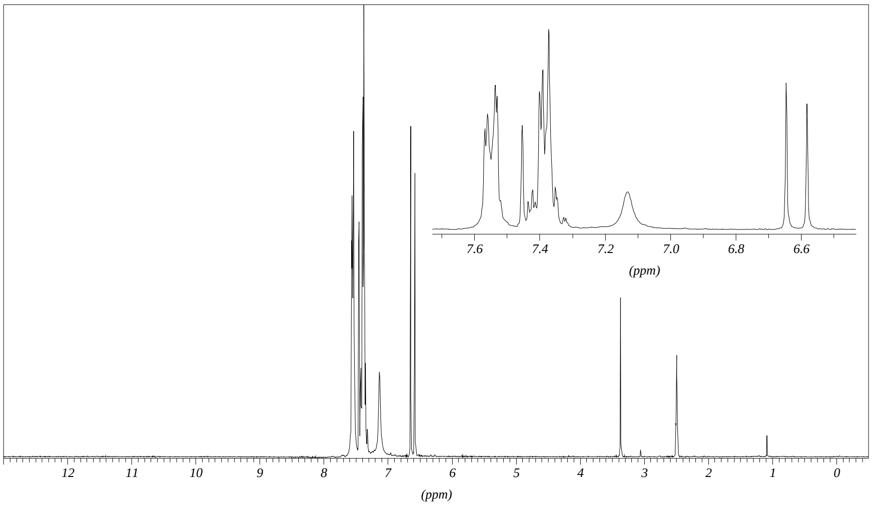


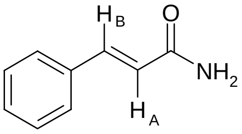
HPLC II of the extract from the acidified aqueous phase



Retention time (min)	Substance	Peak area %	
		HPLC I	HPLC II
13.1	cinnamic acid amide	100	80
17.7	cinnamic acid		20

^{1}H NMR spectrum of the pure product (250 MHz, DMSO-D$_6$)

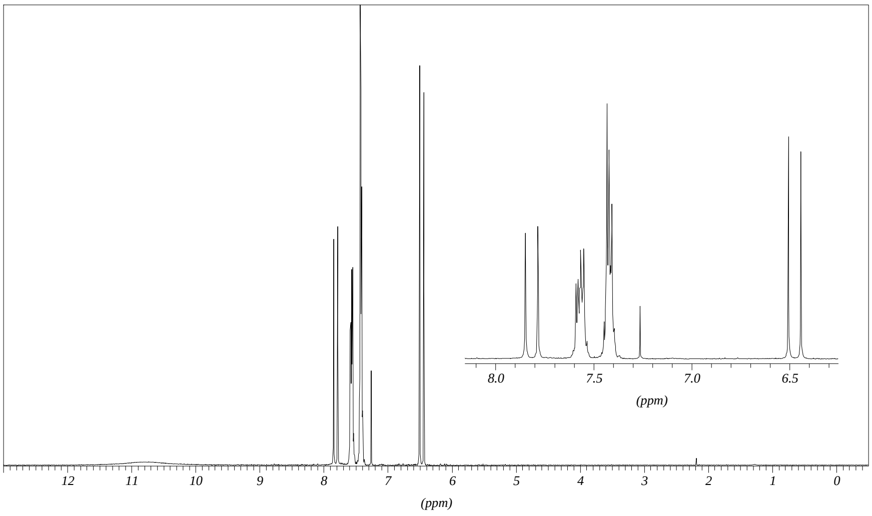


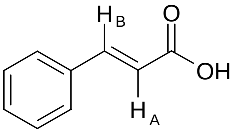


δ (ppm)	Multiplicity	Coupling constant (Hz)	Number of H	Assignment
6.61	d	J_{AB} = 15.9	1	H_A
7.13	wide s		1	NH (only one)
7.2 – 7.6	m		7	NH + CH aromatic +H_B
within the multiplett: 7.42	d	J_{AB} = 15.9	1 of 7	H_B

The signals at ppm < 4 originate from DMSO, water and *tert*-butyl methyl ether.

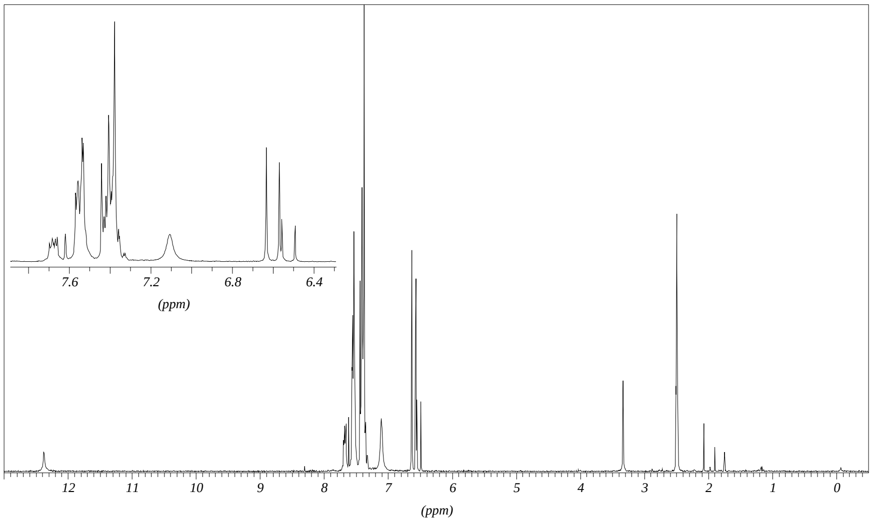
^{1}H NMR spectrum of the cinnamic acid (250 MHz, CDCl$_3$) (for comparison)



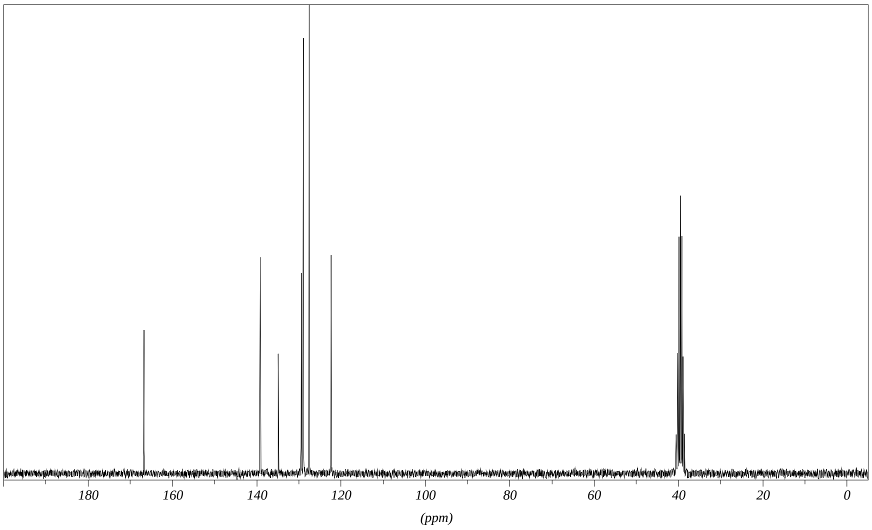


δ (ppm)	Multiplicity	coupling constant (Hz)	Number of H	Assignment
6.48	d	J_{AB} = 16.0	1	H_A
7.35 – 7.65	m		5	CH arene
7.82	d	J_{AB} = 16.0	1	H_B
10.8	broad s		1	OH

^{1}H NMR spectrum of the extract from the acidified aqueous phase
(mixture of cinnamic acid amide and cinnamic acid) (250 MHz, DMSO-D$_6$)

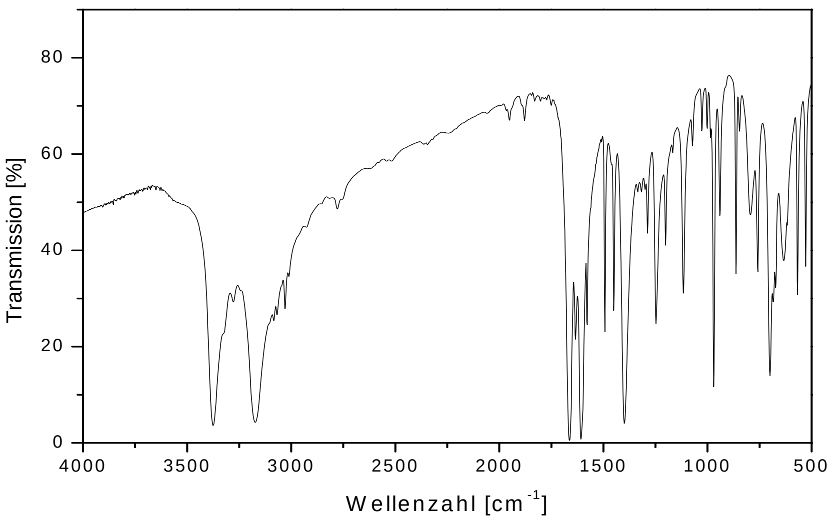


^{13}C NMR spectrum of the pure product (cinnamic acid amide) (250 MHz, DMSO-D$_6$)



δ (ppm)	Assignment
122.31	= **C**H – CONH$_2$
127.52	**C**H arene
128.90	**C**H arene
129.42	**C**H arene
134.86	**C**$_{quart}$ arene
139.16	**– C**H = CH – CONH$_2$
166.68	**– C**ONH$_2$
38.5-40.5	solvent

IR spectrum of the pure product (KBr)



(cm^{-1})	**Assignment**
3375, 3175	N – H – valence
3084	= C – H – valence,
1665	C = O – valence, amide
1634	
1610	C = C – valence, alkene
1580, 1495	C = C – valence, arene
1450	