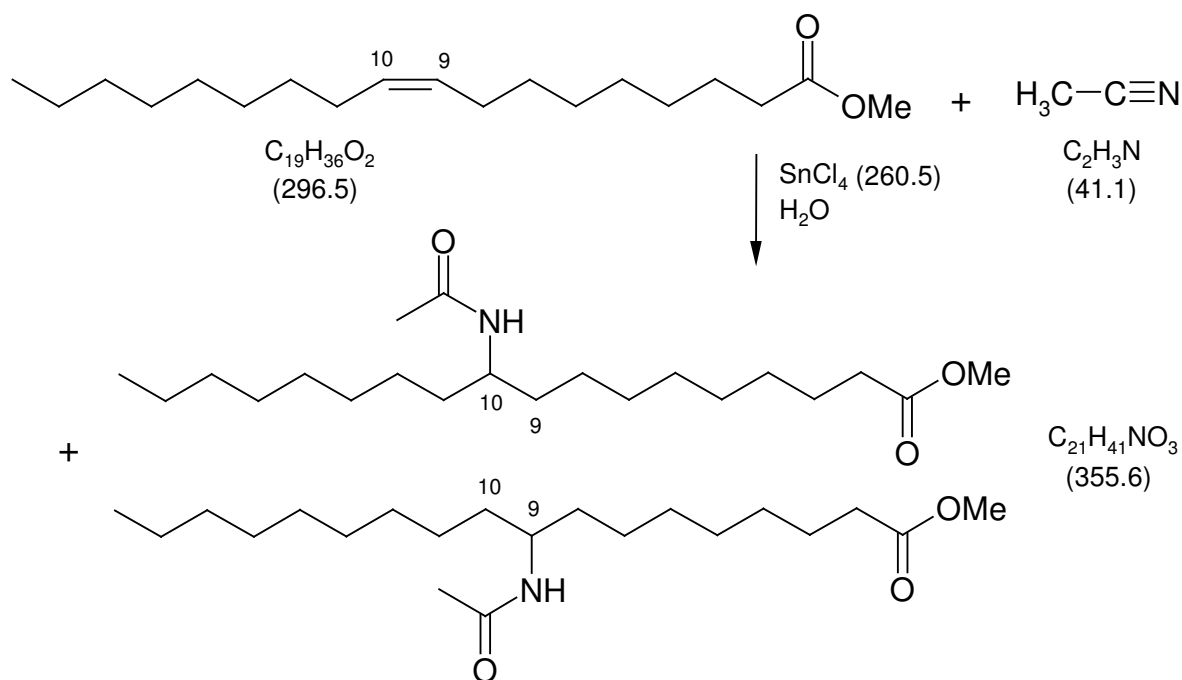


4019 Synthesis of acetamidostearic acid methyl ester from oleic acid methyl ester



Classification

Reaction types and substance classes

addition to alkenes, Ritter reaction
 carboxylic acid ester, renewable resources

Work methods

stirring with magnetic stir bar, adding dropwise with an addition funnel, heating under reflux, shaking out, extracting, recrystallizing, filtering, evaporating with rotary evaporator, use of a cooling bath, heating with oil bath

Instruction (batch scale 8.4 mmol)

Equipment

10 mL two-neck flask, addition funnel with pressure balance, internal thermometer, heatable magnetic stirrer, magnetic stir bar, reflux condenser, separating funnel, rotary evaporator, ice sodium chloride cooling bath, oil bath,

Substances

oleic acid methyl ester (purity 84%) (bp 218 °C)	3.0 g (8.4 mmol pure ester)
acetonitrile (bp 82 °C)	0.66 g (16 mmol)
tin(IV)-chloride (bp 114 °C)	3.1 g (12 mmol)
water	180 mg (10 mmol)

<i>tert</i> -butyl methyl ether (bp 55 °C)	150 mL
sodium hydrogen carbonate	about 4 g (for 40 mL saturated aqueous solution)
sodium sulfate for drying	
methanol/water (5:2) for recrystallization	

Reaction

3.0 g (8.4 mmol) adipic acid methyl ester (purity 84%) and 0.66 g (16 mmol) acetonitrile are filled in a 10 mL two-neck flask equipped with magnetic stir bar, addition funnel and internal thermometer. The reaction flask is cooled down to -18°C internal temperature in an ice sodium chloride mixture. With an addition funnel 3.1 g (12 mmol) tin tetrachloride are added dropwise within 5 minutes under stirring. During the addition the internal temperature rises from -18 to +30 °C. Afterwards 180 mg (10 mmol) water are added dropwise. The internal thermometer and the addition funnel are removed, a reflux condenser is installed and the mixture is heated under stirring for 4 hours at 70 °C.

Work up

After cooling down the reaction solution is transferred in a separating funnel with 150 mL *tert*-butyl methyl ether and shaken out with 40 mL water. Then the separated organic phase is shaken out with 40 mL saturated sodium hydrogen carbonate solution, washed four times with 40 mL water each and dried with sodium sulfate. After the drying agent has been filtered off and the solvent has been evaporated at the rotary evaporator, the crude product remains as a brownish-white solid. Crude yield: 3.25 g

The crude product is recrystallized from methanol/water (5 : 2).

Yield: 2.50 g (7.03 mmol, 84%); white solid, mp 74 – 75 °C

Comments

Excess of acetonitrile and tin tetrachloride is used. If stoichiometric quantities are used, the reaction needs 12 hours to be finished.

Mass spectrometry studies show, that the isolated product is a mixture of regioisomers. Besides the 9- and 10-acetamido stearic acid methyl ester also in 7-, 8-, 11- and 12-position substituted products are formed to a small extent.

Waste management

Recycling

tert-butyl methyl ether is collected and redistilled.

Waste disposal

Waste	Disposal
aqueous phases (also containing acetonitrile)	solvent water mixtures, containing halogen
methanol water mother liquor	solvent water mixtures, halogen free
sodium sulfate	solid waste, free from mercury

Time

5 hours for the reaction
about 4 hours for work up

Break

After dissolving the reaction mixture in *tert*-butyl methyl ether and addition of water

Degree of difficulty

Medium

Instruction (batch scale 84 mmol)**Equipment**

250 mL two-neck- or three-neck flask, addition funnel with pressure balance, internal thermometer, heatable magnetic stirrer, magnetic stir bar, reflux condenser, separating funnel, rotary evaporator, ice sodium chloride cooling bath, oil bath

Substances

oleic acid methyl ester (purity 84%) (bp 218 °C)	30.0 g (84.0 mmol pure ester)
acetonitrile (bp 82 °C)	6.58 g (160 mmol)
tin(IV)-chloride (bp 114 °C)	31.0 g (120 mmol)
water	1.80 g (100 mmol)
<i>tert</i> -butyl methyl ether (bp 55 °C)	600 mL
sodium hydrogen carbonate	about 10 g (for 100 mL saturated aqueous solution)
sodium sulfate for drying	
methanol/water (5:2) for recrystallization	

Reaction

30.0 g (84.0 mmol) oleic acid methyl ester (purity 84%) and 6.58 g (160 mmol) acetonitrile are filled in a 250 mL three-neck flask equipped with magnetic stir bar, addition funnel and internal thermometer. The reaction flask is cooled down to -18°C internal temperature in an ice sodium chloride mixture. With an addition funnel 31.0 g (120 mmol) tin tetrachloride are added dropwise within 5 minutes under stirring. During the addition the internal temperature rises from -18 to +30°C. Afterwards 180 mg (10 mmol) water are added dropwise. The internal thermometer and the addition funnel are removed, a reflux condenser is installed and the mixture is heated under stirring for 4 hours at 70 °C.

Work up

After cooling down the reaction solution is transferred in a separating funnel with 600 mL *tert*-butyl methyl ether and shaken out with 100 mL water. Then the separated organic phase is shaken out with 100 mL saturated sodium hydrogen carbonate solution, washed five times with 100 mL water each and dried with sodium sulfate. After the drying agent has been

filtered off and the solvent is evaporated at the rotary evaporator, the crude product remains as a brownish-white solid. Crude yield: 32.8 g

The crude product is recrystallized from methanol/water (5 : 2).

Yield: 27.8 g (78.2 mmol, 93%); white solid, mp 74 – 75 °C

Comments

An excess of acetonitrile and tin tetrachloride is used. If stoichiometric quantities are used, the reaction needs 12 hours to be finished.

Mass spectrometry studies show, that the isolated product is a mixture of regioisomers. Besides the 9- and 10-acetamido stearic acid methyl ester also in 7-, 8-, 11- and 12-position substituted products are formed to a small extent.

Waste management

Recycling

tert-butyl methyl ether is collected and redistilled.

Waste disposal

Waste	Disposal
aqueous phases (also containing acetonitrile)	solvent water mixture, containing halogen
methanol water mother liquor	solvent water mixtures, halogen free
sodium sulfate	solid waste, free from mercury

Time

5 hours for the reaction

about 4 hours for work up

Break

After dissolving the reaction mixture in *tert*-butyl methyl ether and addition of water

Degree of difficulty

Medium

Analytics

Reaction monitoring with TLC

Sample preparation:

Using a Pasteur pipette, one drop from the reaction mixture is taken and diluted with 0.5 mL diethylether.

TLC-conditions:

adsorbant: TLC aluminium foil (silica gel 60)

eluent: petroleum ether / acetic acid ethyl ester / methanol (14 : 6 : 0.5)

visualizing agent: The TLC aluminium foil is dipped in 2N H₂SO₄ and then dried with a hot air dryer.

GC

Sample preparation:

10 mg crude or pure product are dissolved in 10 mL dichloromethane.

GC-conditions:

column: DB-1, 28 m, internal diameter 0.32 mm, film 0.25 μm

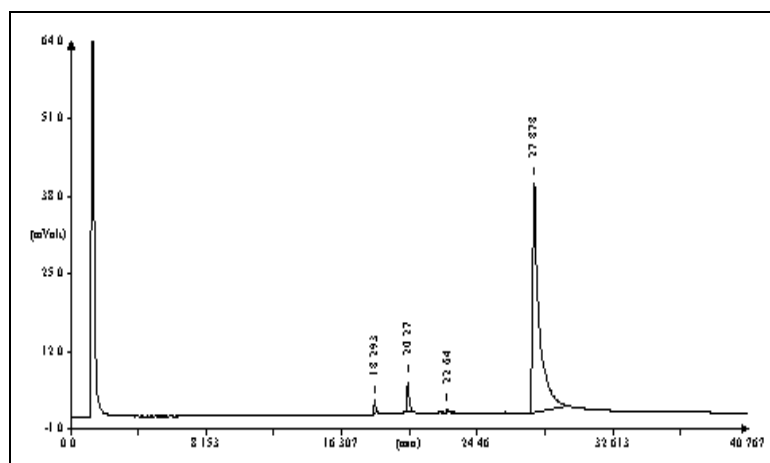
inlet: on-column-injection; injected volume 0.2 μL

carrier gas: hydrogen (40 cm/sec)

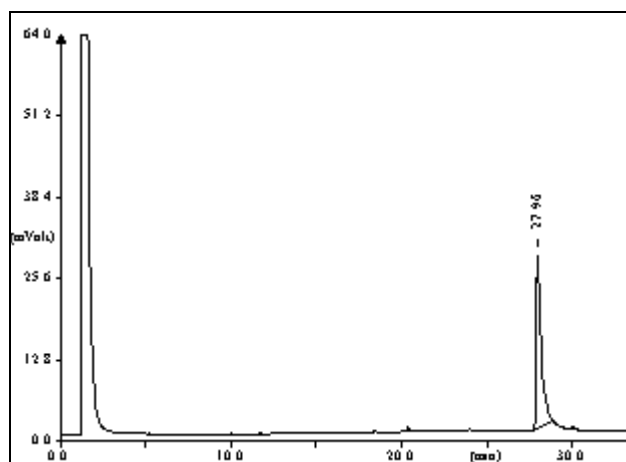
oven: 90 $^{\circ}\text{C}$ (5 min), 10 $^{\circ}\text{C}/\text{min}$ at 240 $^{\circ}\text{C}$ (35 min)

detector: FID, 270 $^{\circ}\text{C}$

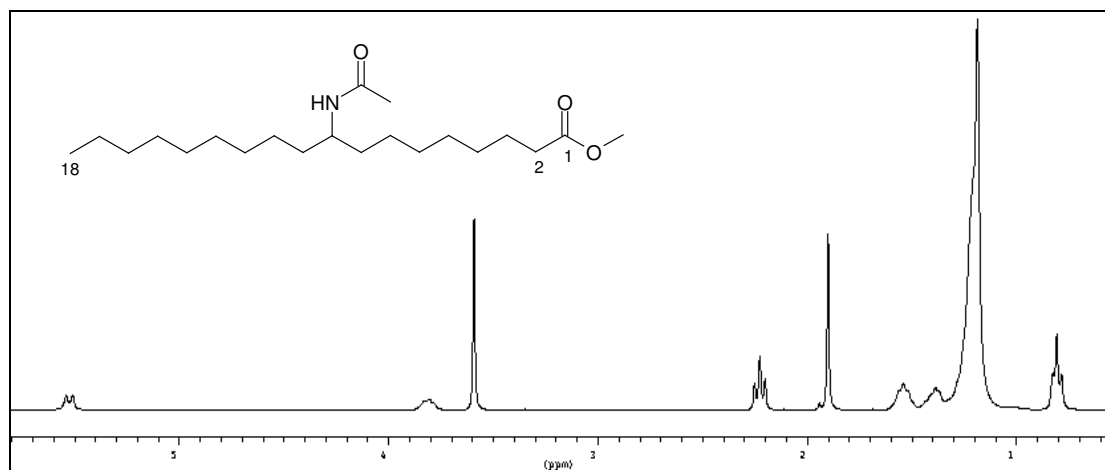
Percent concentration was calculated from peak areas.

GC of the crude product

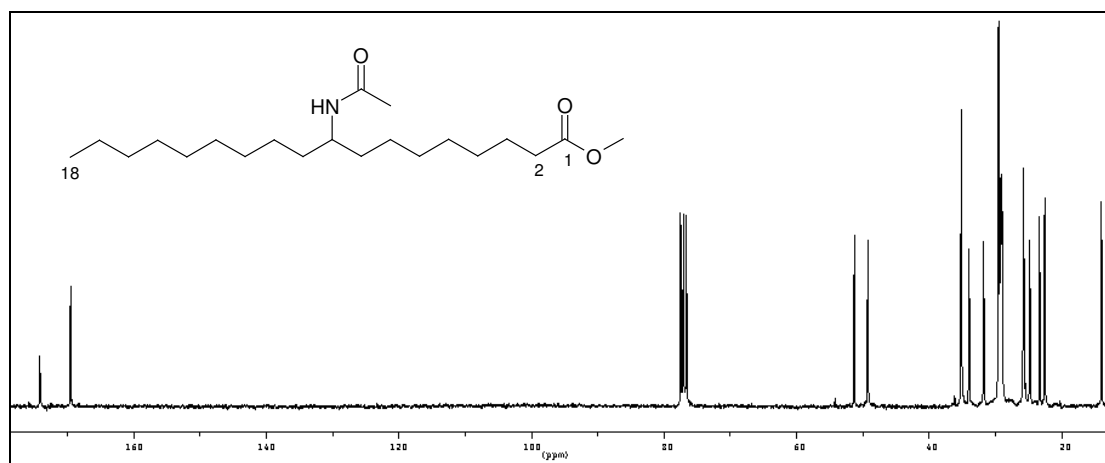
Retention time (min)	Substance	Peak area %
27.99	product (mixture of regioisomers)	97.4
20.34	stearic acid methyl ester	1.84
18.36	palmitic acid methyl ester	0.74

GC of the pure product

Retention time(min)	Substance	Peak area %
27.96	product (mixture of regioisomers)	100

¹H NMR spectrum of the product (mixture of regioisomers) (300 MHz, CDCl₃)

δ (ppm)	Multiplicity	Number of H	Assignment
0.81	T	3	18-H
1.1-1.6	M	28	remaining CH ₂
1.90	S	3	-NH-C(=O)-CH ₃
2.23	T	2	2-H
3.59	S	3	-O-CH ₃
3.80	M	1	-CH-NH-
5.52	D	1	-NH-

¹³C NMR spectrum of the pure product (mixture of regioisomers) (75.5 MHz, CDCl₃)

δ (ppm)	Assignment
174.2	C-1
169.5	NH-C(=O)-
51.3	O-CH ₃
49.2	-CH-NH-
35.1	-CH ₂ -CH-NH-
34.0	C-2
76.5-77.5	solvent