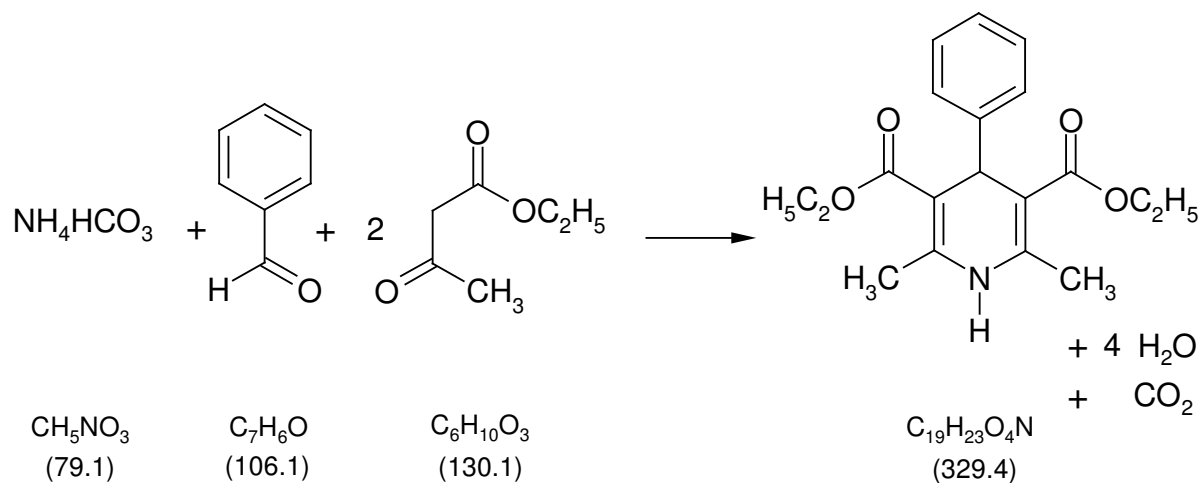


5013 Synthesis of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester



Literature

Hinkel, L. E., Ayling, E. E. Morgan, W. H., *J. Chem. Soc.*, **1931**, 1835

Classification

Reaction types and substance classes

reaction of the carbonyl group in aldehydes, reaction of the carbonyl group in ketones, Hantzsch synthesis, ring closure reaction
 carboxylic acid ester, aldehyde, ketone, heterocycle, aromatics

Work methods

microwave-assisted reaction, heating under reflux, filtering, evaporating with rotary evaporator, stirring with magnetic stir bar, draining of gases

Instruction (batch scale 100 mmol)

Equipment

Microwave system ETHOS 1600, 500 mL two-neck flask, 50 mL round bottom flask, magnetic stirrer, magnetic stir bar, reflux condenser, glass tube (40 cm, NS 29), adapter with ground glass joint and hose coupling, suction flask, 2 wash bottles, Buechner funnel (diameter 6 cm), rotary evaporator, desiccator

Substances

benzaldehyde (bp 179 °C)	10.6 g (10.1 mL, 100 mmol)
acetoacetic acid ethyl ester (bp 180 °C)	28.6 g (27.8 ml, 220 mmol)
ammonium hydrogen carbonate	9.88 g (125 mmol)
ethanol (bp 78 °C)	100 mL
<i>tert</i> -butyl methyl ether (bp 55 °C)	40 mL

Reaction

The reaction apparatus consists of a 500 mL two-neck flask with magnetic stir bar, electronic temperature control and reflux condenser. The reflux condenser is connected with an adapter with ground glass joint and hose coupling and a hose for draining of the gases forming during reaction. The hose is connected with an empty safety wash bottle which is connected with a wash bottle, filled with about 300 mL of water.

10.6 g (10.1 mL, 100 mol) benzaldehyde, 28.6 g (27.8 mL, 220 mmol) acetoacetic acid ethyl ester, 9.88 g (125 mmol) ammonium hydrogen carbonate and 40 mL ethanol are filled in the reaction flask. The reaction apparatus is installed with the glass tube in the micro wave system (see "Technical instructions: Standard refluxing apparatus for micro wave systems") and treated for 40 minutes: The mixture is heated with 900 W in 2 minutes to 80 °C and this temperature is kept for 20 minutes with 400 W, then with 700 W with a temperature ramp in 3 minutes from 80 °C to 88 °C until continuously refluxing and this temperature is kept for 15 minutes with 500 W. Afterwards the reaction mixture is further stirred for 30 minutes without additional energy supply.

Work up

Until its complete crystallization the cooled reaction mixture is kept in the cooler overnight where the crude product crystallizes as light-yellow solid material. The crude product is finely chopped in the flask and sucked off over a Buechner funnel. On the Buechner funnel it is washed with 10 mL, 20 mL and 10 mL ethanol and sucked off.

A second product fraction can be gained from the filtrate:

The solvent is evaporated from the filtrate at the rotary evaporator and the remaining oily crystalline paste is stirred with 30 mL *tert*-butyl methyl ether for 15 minutes. The solid material is filtered over a folded filter paper and washed repeatedly with 10 mL *tert*-butyl methyl ether. The yellowish residue is transferred in a 50 mL flask and stirred with 20 mL ethanol for 15 minutes, then sucked off over a Buechner funnel, washed with less ethanol and sucked off again.

The two product fractions are dried in the desiccator at reduced pressure.

Yield (total): 21.1 g (64.1 mmol, 64%); mp 156-158 °C; GC-purity of both fractions 100%.

The first product fraction is colourless and finely crystalline, the second pale-yellow.

Comments

An aqueous solution of ammonia was not used for the reaction since a high water concentration in the system is disadvantageous for the reaction. From the used ammonium hydrogen carbonate in the temperature area of 80 °C the ammonia necessary for the reaction is released. A larger excess of ammonia does not lead to an increase in yield.

Waste management**Recycling**

The evaporated ethanol is collected and redistilled.

Waste disposal

Waste	Disposal
<i>tert</i> -butyl methyl ether filtrate	organic solvents, halogen free
ethanol filtrates and washing solutions	organic solvents, halogen free

Time

2 - 3 hours (without drying time)

Break

Before work-up

After isolation of the first product fraction

Degree of difficulty

Easy

Analytics**GC**

Sample preparation:

50 mg of a sample are dissolved in 1 mL dichloromethane from which 3 μ L are injected.

GC-conditions:

column: HP-5; length 30 m, internal diameter 0.32 mm, film 0.25 μ m

inlet: split injection 194:1

carrier gas: H₂, pre-column pressure 31 kPa

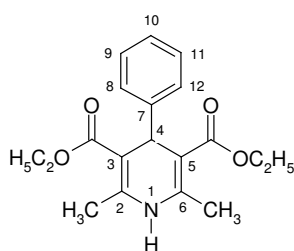
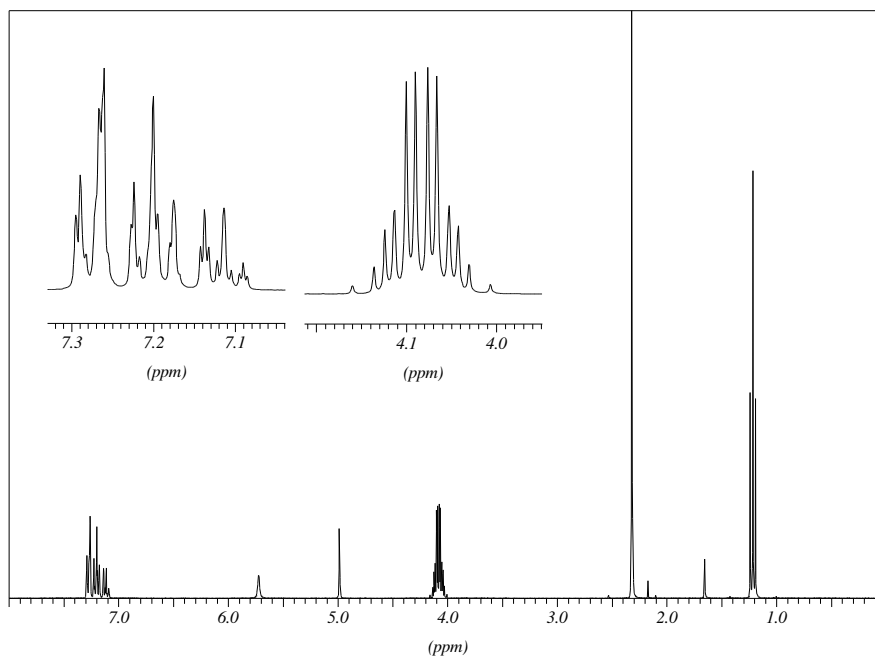
oven: 3 min isotherm at 50 °C, afterwards with 8 °C/min to 320 °C

detector: 300 °C

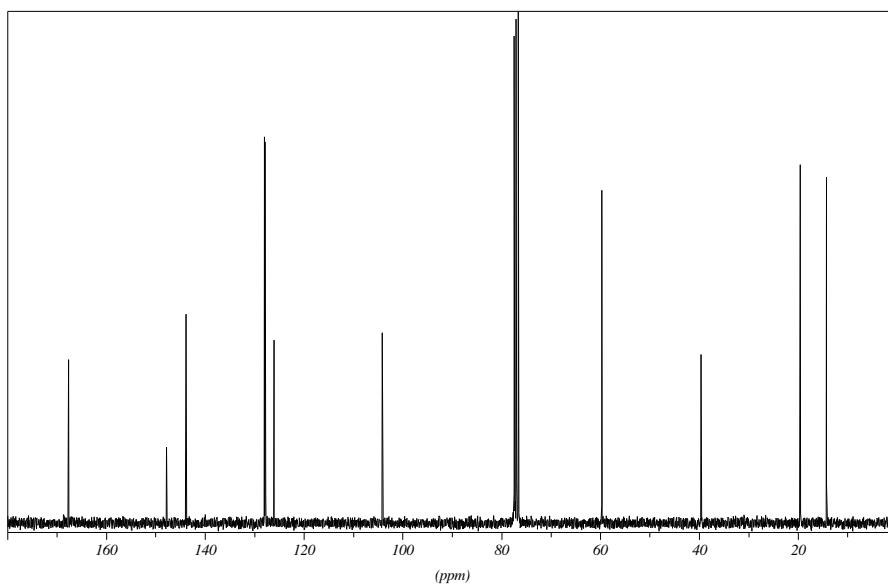
Percent concentration was calculated from peak areas.

GC of the pure product

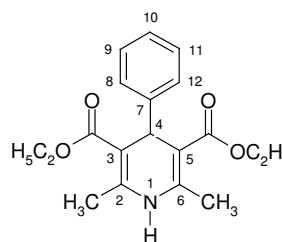
Retention time of the product = 29 min. No impurities were detected.

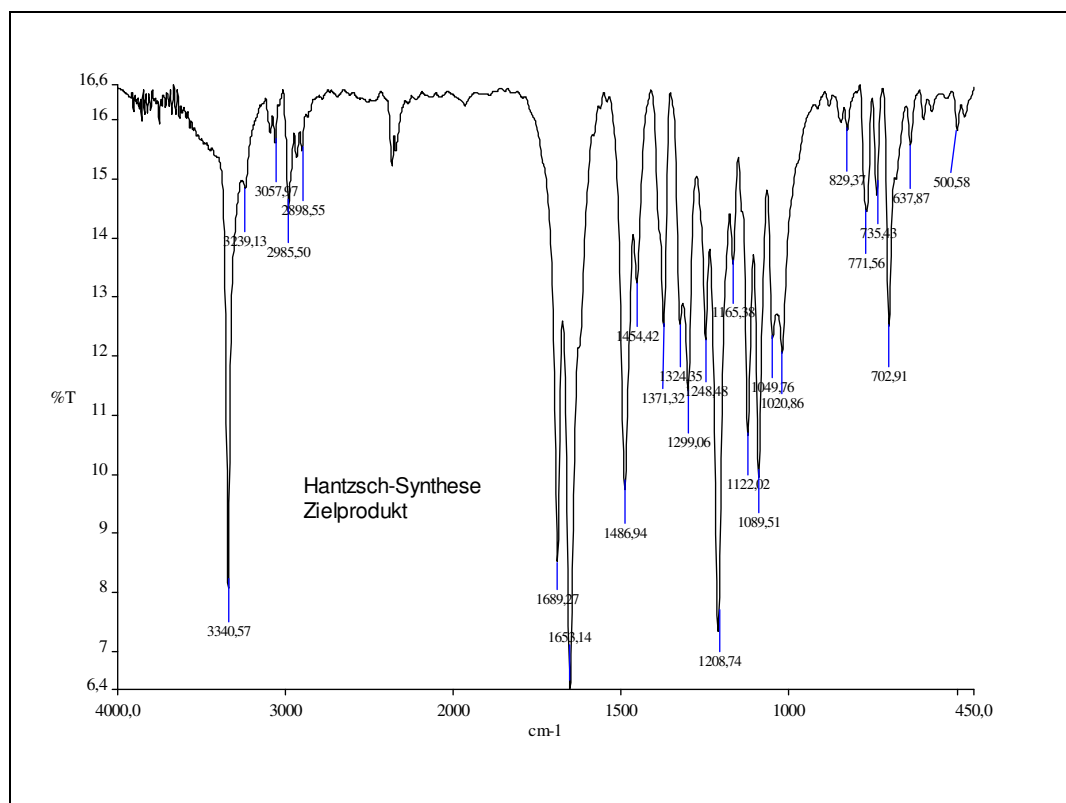
^1H NMR spectrum of the product (300 MHz, CDCl_3)

δ (ppm)	Multiplicity	Number of H	Assignment
1.22	t	6	$\text{CH}_2\text{-CH}_3$
2.32	s	6	CH_3 (at the ring)
4.08	m	4	$\text{CH}_2\text{-CH}_3$
4.99	s	1	4-H
5.72	s	1	NH
7.07-7.30	m	5	CH arene

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

δ (ppm)	Assignment
167.65	C=O
147.76	C-7
143.87	C-2, C-6
127.99, 127.82	C-8, C-12, C-9, C11
126.09	C-10
104.14	C-3, C-5
59.72	O-CH ₂ -
39.62	C-4
19.55	CH ₃ at the ring
14.24	CH ₃ -CH ₂ -
76.5-77.5	solvent



IR-spectrum of the product (KBr)

(cm ⁻¹)	Assignment
3340	N-H- valence
3080, 3060	C-H-valence, arene
2985, 2900	C-H-valence, alkane
1690	C=O-valence, ester
1655	C=C-valence, alkene
1490	C=C-valence, arene