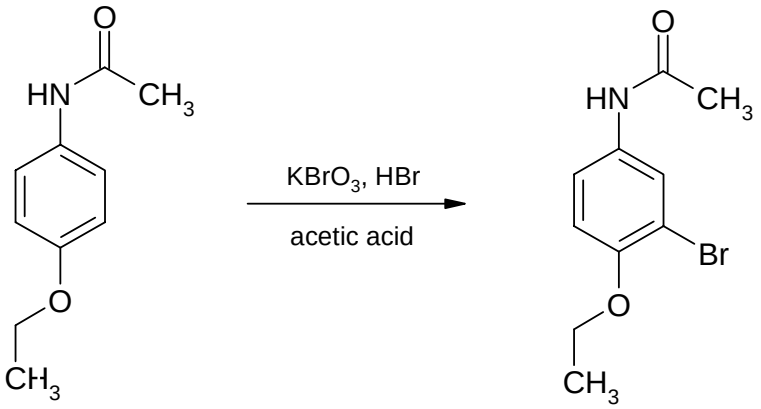
1006 Bromination of 4-ethoxyacetanilide (phenacetin) to 3-bromo-4-ethoxyacetanilide



$C_{10}H_{13}NO_2$ (179.2) (167.0) (80.9) $C_{10}H_{12}BrNO_2$ (258.1)

Literature

P.F. Schatz, *J. chem. Educ.* **1996**, 73, 267

Classification

Reaction types and substance classes

electrophilic substitution of aromatics, bromination

aromatics, bromoaromatics, aryl ether

Work methods

stirring with magnetic stir bar, adding dropwise with an addition funnel, filtering, recrystallizing, heating with oil bath

Instruction (batch scale 100 mmol)

Equipment

500 mL Erlenmeyer flask, 1 L beaker, heatable magnetic stirrer, magnetic stir bar, internal thermometer, addition funnel, Buechner funnel, suction flask, 250 mL round-bottom flask, reflux condenser, desiccator, oil bath

Substances

4-ethoxyacetanilide (mp 133-136 °C)	17.9 g (100 mmol)
potassium bromate	5.56 g (33.3 mmol)
hydrobromic acid (48%) (bp 126 °C)	29.8 g (20 mL, 177 mmol)
acetic acid (bp 118 °C)	135 mL

aqueous sodium disulfite solution (0.2 M)	60 mL
methanol (bp 65 °C)	about 80 mL
ice	

Reaction

In a 500 mL Erlenmeyer flask with magnetic stir bar and internal thermometer 17.9 g (100 mmol) 4-ethoxyacetanilide are dissolved in 135 mL acetic acid under stirring. 5.56 g (33.3 mmol) potassium bromate are added to the solution. Then 29.8 g (20 mL, 177 mmol) hydrobromic acid are added dropwise under stirring at room temperature. The mixture is stirred for further 30 minutes at room temperature.

Work up

The brown clear solution is filled in a 1 L beaker containing 300 mL ice water, the product precipitates as a light solid. The mixture is stirred for further 15 minutes. The precipitation is sucked off over a Buechner funnel, stirred with a glass rod in a beaker containing 60 mL 0.2 M sodium sulfite solution, sucked off again, washed on the filter with 100 mL water, sucked off and dried in the desiccator.
Crude yield: 26.7 g; GC purity 89% (see analytics)

The crude product is recrystallized from methanol/water (3:1) and dried in the desiccator.

Yield: 19.1 g (74.0 mmol, 74%); colourless crystalline substance, mp 110-111 °C; GC-purity 98%

Waste management

Waste disposal

Waste	Disposal
aqueous filtrates	reduction of possibly contained bromine with sodium disulfite solution, then: solvent water mixtures,containing halogen
mother liquor from recrystallization	solvent water mixtures, containing halogen

Time

3-4 hours, without time for drying

Break

Before recrystallization

Degree of difficulty

Easy

Instruction (batch scale 30 mmol)

Equipment

250 mL Erlenmeyer flask, 600 mL beaker, magnetic stirrer, magnetic stir bar, internal thermometer, addition funnel, Buechner funnel, suction flask, 100 mL round-bottom flask, reflux condenser, desiccator, oil bath

Substances

4-ethoxyacetanilide (mp 133-136 °C)	5.38 g (30.0 mmol)
potassium bromate	1.67 g (10.0 mmol)
hydrobromic acid (48%) (bp 126 °C)	8.9 g (6.0 mL, 53 mmol)
acetic acid (bp 118 °C)	40 mL
aqueous sodium disulfite solution (0.2 M)	20 mL
methanol (bp 65 °C)	etwa 20 mL
ice	

Reaction

In a 250 mL Erlenmeyer flask with magnetic stir bar and internal thermometer 5.38 g (30.0 mmol) 4-ethoxyacetanilide are dissolved under stirring in 40 mL acetic acid. 1.67 g (10.0 mmol) potassium bromateare added to the solution. Then 8.9 g (6.0 mL, 53 mmol) hydrobromic acid are added dropwise under stirring at room temperature. The mixture is stirred for further 30 minutes at room temperature.

Work up

The brown clear solution is filled in a 600 mL beaker containing 100 mL ice water, the product precipitates as light solid. The mixture is stirred for further 15 minutes. The precipitation is sucked off over a Buechner funnel, stirred with a glass rod in a beaker with 20 mL 0.2 M sodium disulfite solution, sucked off again, washed on the filter with 100 mL water, sucked off and dried in the desiccator.
Crude yield: 9.27 g; GC purity 89% (see analytics)

The crude product is recrystallized from methanol / water (3:1) and dried in the desiccator.
Yield: 4.5 g (17.4 mmol, 58%); colourless crystalline substance, mp 110-111 °C; GC-purity 98%

Waste management

Waste disposal

Waste	Disposal
aqueous filtrates	reduction of possibly contained bromine with sodium disulfite solution, then: solvent water mixtures, containing halogen
mother liquor from recrystallization	solvent water mixtures, containing halogen

Time
3-4 hours without time for drying

Break
Before recrystallization

Degree of difficulty
Easy

Analytics

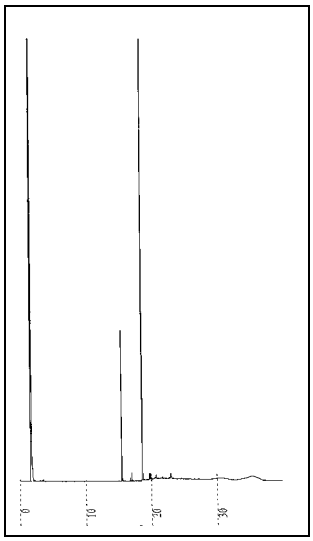
GC

GC conditions:

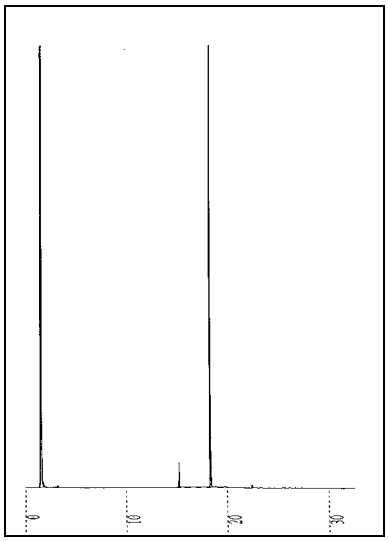
column:	5CB Low Blend/MS, length 30 m, internal diameter 0.32 mm, film 0.25 µm
inlet:	injector temperature 210 °C, split injection, injected volume 1 µL
carrier gas:	H_2, pre-column pressure 50 kPa
oven:	60 °C (2 min), heating rate 10 °C/min, isotherme 240 °C (30 min)
detector:	FID, 310 °C
integrator:	Shimadzu

Percent concentration was calculated from peak areas.

GC of the crude product



GC of the pure product

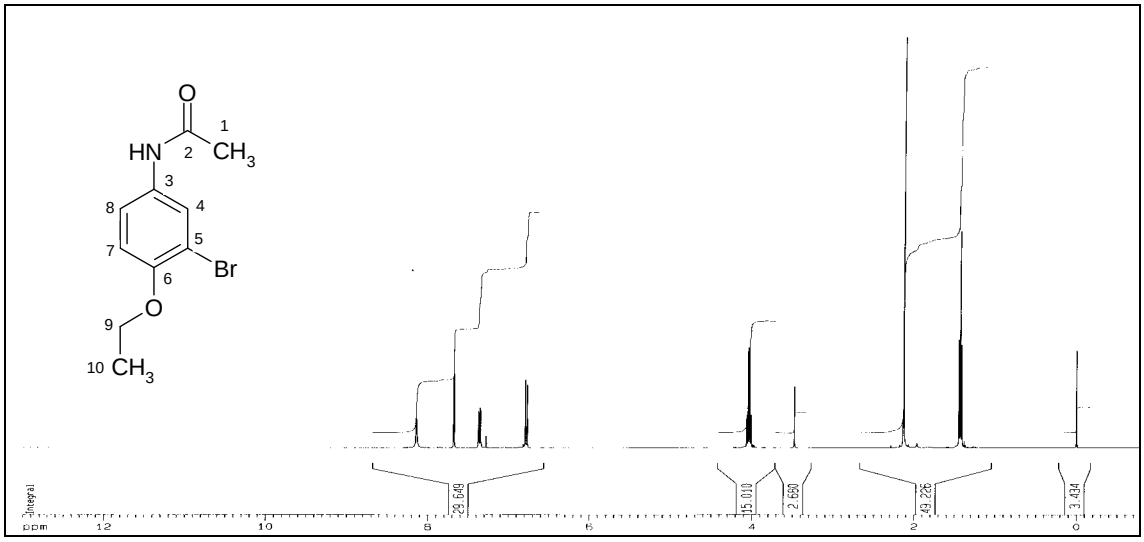


Retention time (min)	Substance	Peak area %	
		crude product	pure product
18.5	product (3-bromo-4-ethoxyacetanilide)	89.6	98
15.6	educt (4-ethoxyacetanilide)	10.4	

Traces of 2-bromo-4-ethoxyacetanilide and of double-brominated side products could be determined in the product.

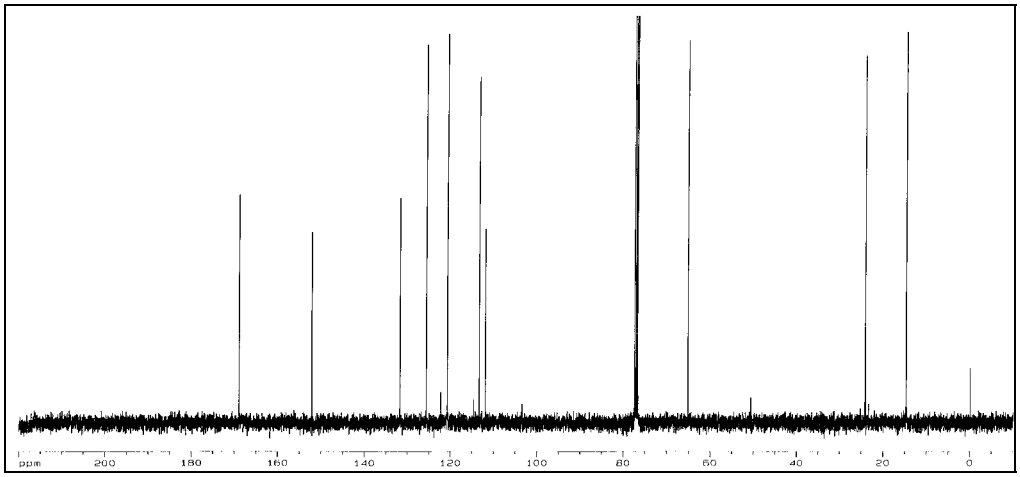
^{1}H NMR spectrum of the crude product (400 MHz, $CDCl_3$)

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

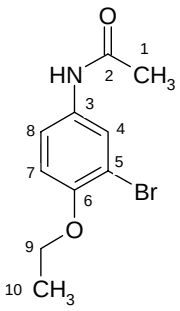


δ (ppm)	Multiplicity	Number of H	Assignment
1.43	t	3	10-H
2.13	s	3	1-H
4.03	q	2	9-H
6.77	dd	1	7-H
7.35	dd	1	8-H
7.68	dd	1	4-H
8.13	s	1	NH
7.26			solvent

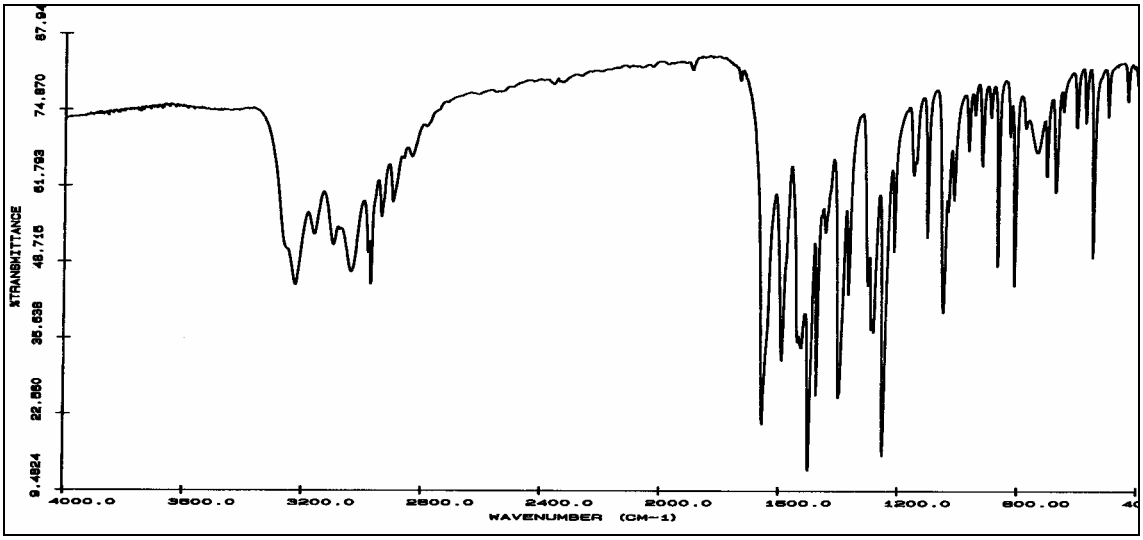
^{13}C NMR spectrum of the pure product (100 MHz, $CDCl_3$)



δ (ppm)	Assignment
14.64	C-10
24.06	C-1
65.11	C-9
111.87	C-5
113.31	C-7
120.71	C-8
125.61	C-4
131.73	C-3
152.12	C-6
168.91	C-2
76.5-77.5	solvent



IR spectrum of the pure product (KBr)



(cm^{-1})	**Assignment**
3225 – 3165	N-H-valence
3100 - 3040	C-H-valence, arene
2980 - 2840	C-H-valence, alkane
1655	C=O-valence, carbon acid amide
1500	C=C-valence, arene