A Simple One-Step Synthesis of Substituted Methyl 2-Benzoylamino-3-arylaminopropenoates, Intermediates in the Preparation of Substituted Arylaminoalanines[1)]

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A simple one-step synthesis of substituted methyl 2-benzolamino-3-anilino-propenoates **8a-r** from substituted anilines **7a-r** and methyl 2-benzoylamino-3-dimethylaminopropenoates **6** is described.

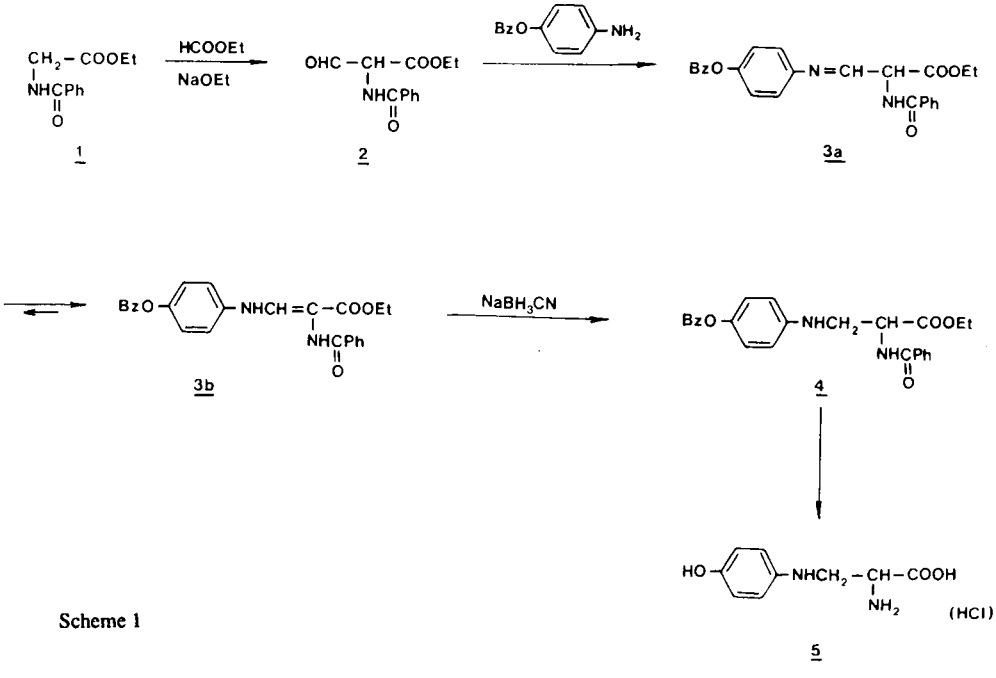
Eine einfache, einstufige Synthese substituierter 2-Benzoylamino-3-aryl-aminopropensäuremethylester, Zwischenprodukte für die Herstellung substituierter Arylaminoaniline

Eine einfache, einstufige Synthese der substituierten 2-Benzoylamino-3-aryl-aminopropensäuremethylester **8a-r** aus den substituierten Anilin-Derivaten **7a-r** und 2-Benzoylamino-3-dimethylaminopropensäuremethylester **6** wird beschrieben.

Recently, a selective antitumor activity of L-glutamic acid ß-(4-hydroxy)-anilide, a natural product isolated from *Agaricus bisporus*, has been reported[2,3,4)]. The mechanism of action is based on enzymatic hydroxylation by tyrosinase and further oxidation of this compound into 2-hydroxy-4-iminoquinone,[5)] which interacts with α-DNA polymerase so inhibiting the tumor growth[6)].

On this basis the synthesis and antitumor activity of ß-[(p-hydroxyphenyl)amino]alaline hydrochloride (**5**) and some other compounds has been described[7)]. The synthesis of **5** is a multi-step procedure starting from ethyl hippurate (**1**) which has been formylated according to *Erlenmeyer* and *Kreutz* to give formylpyruvate (**2**) and further transformed with p-benzyloxy-aniline into ethyl 2-benzoylamino-3-(p-benzyloxy-anilino)-propenoate **3**. This, when treated with $NaBH_3CN$ produced ethyl 2-benzoylamino-3-(p-benzyloxy-anilino)-propanoate (**4**) which was finally converted by acid hydrolysis into **5** [7)] (Scheme 1).

In our studies in the field of heteroaryl substituted α-amino acids[8,9,10,11)] we prepared 2-benzoylamino-3-heteroarylaminopropenoates in two different ways, either by transformation of N'-heteroaryl-N,N-dimethylformamidines into heteroarylaminomethyleneoxazolones followed by opening of the oxazolone ring, or by reaction of heterocyclic amines with 2-benzoylamino-3-dimethylaminopropenoates under acidic conditions[9,10,11)]. The latter reaction represents a simple one-step reaction for the preparation of compounds **8**, the key-intermediates in the synthesis of



Scheme 1

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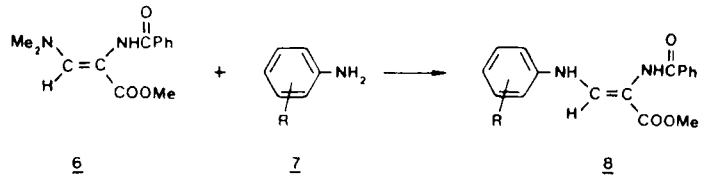
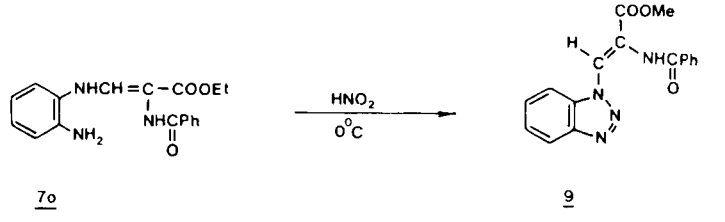


6 7 8

7r 8r

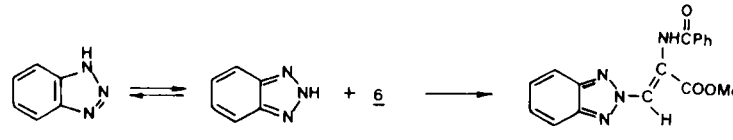
	R
a	2 - OH
b	4 - OH
c	2 - NO_2
d	3 - NO_2
e	4 - NO_2
f	2,4 - di - NO_2
g	2 - Me, 3 - NO_2
h	2 - Me
i	3 - Me
j	4 - Me
k	2,6 - di - Me
l	3 - COOH
m	4 - COOH
n	4 - COOEt
o	2 - NH_2
p	2 - COPh
q	3 - COPh

Scheme 2



7o 9

Scheme 3



a 10 b 11

substituted ß-anilino-alanines. Namely, by heating of substituted anilines 7 with methyl 2-benzoylamino-3-dimethylaminopropenoate (**6**) in ethanol in the presence of HCl the corresponding substituted 3-anilino-2-benzoylaminopropenoates **8** are formed in moderate to good yields. In this connection, hydroxy, nitro, methyl, carboxy, ethoxycarbonyl, amino, and benzoyl substituted anilines **7a-q**, and α-naphthylamine (**7r**) were used. (Scheme 2). The method is advantageous in comparison to the procedure described previously[7], since hydroxy, amino and carboxy groups

Table 1: Experimental and Analytical Data

Compound	Reaction time (h)	Yield [a] (%)	m.p.(°C) solvent for crystallization	Molecular formula	Analysis	C	H	N
8a	2	20	219-222	$C_{17}H_{16}N_2O_4$	Calcd.	65.4	5.16	9.0
			ethanol	(312.3)	Found	65.3	5.39	8.8
8b	1	41	231-233	$C_{17}H_{16}N_2O_4$	Calcd.	65.4	5.16	9.0
			ethanol	(312.3)	Found	65.4	5.18	9.0
8c	8	40	181-182	$C_{17}H_{15}N_3O_5$	Calcd.	59.8	4.43	12.3
			ethanol	(341.3)	Found	59.9	4.40	12.5
8d	6	67	195-196	$C_{17}H_{15}N_3O_5$	Calcd.	59.8	4.43	12.3
			ethanol	(341.3)	Found	59.9	4.43	12.2
8e	4.5	39	240-241	$C_{17}H_{15}N_3O_5$	Calcd.	59.8	4.43	12.3
			ethanol	(341.3)	Found	59.7	4.58	12.1
8f	7	10	225-227	$C_{17}H_{14}N_4O_7$	Calcd.	52.8	3.65	14.5
			ethanol	(386.3)	Found	52.6	3.70	14.6
8g	8	68	182-183	$C_{18}H_{17}N_3O_5$	Calcd.	60.8	4.82	11.8
			ethanol	(355.3)	Found	60.8	4.86	11.9
8h	8.5	48	150-152	$C_{18}H_{18}N_2O_3$	Calcd.	69.7	5.84	9.0
			ethanol	(310.3)	Found	69.4	5.93	9.1
8i	8	56	199-201	$C_{18}H_{18}N_2O_3$	Calcd.	69.7	5.84	9.0
			ethanol	(310.3)	Found	69.6	6.00	9.1
8j	6	55	218-221	$C_{18}H_{18}N_2O_3$	Calcd.	69.7	5.84	9.0
			ethanol	(310.3)	Found	69.8	5.98	9.0
8k	25	56	102-105	$C_{19}H_{20}N_2O_3$	Calcd.	70.3	6.21	8.6
			ethanol	(324.4)	Found	70.4	6.41	8.6
8l	1	74	253-256	$C_{18}H_{16}N_2O_5$	Calcd.	63.5	4.74	8.2
			ethanol	(340.2)	Found	63.4	4.88	8.5
8m	1	59	162-165	$C_{18}H_{16}N_2O_5$	Calcd.	63.5	4.74	8.2
			ethanol	(340.2)	Found	63.8	4.88	8.4
8n	3	70	169-171	$C_{20}H_{20}N_2O_5$	Calcd.	65.2	5.47	7.6
			ethanol	(368.4)	Found	65.3	5.41	7.4
8o	4	50	213-215	$C_{17}H_{17}N_3O_3$	Calcd.	65.6	5.50	13.5
			ethanol	(311.3)	Found	65.7	5.63	13.5
8p	7	28	153-154	$C_{24}H_{20}N_2O_4$	Calcd.	72.0	5.03	7.0
			ethanol	(400.4)	Found	71.6	5.07	6.8
8q	4	31	165-166	$C_{24}H_{20}N_2O_4$	Calcd.	72.0	5.03	7.0
			ethanol	(400.4)	Found	71.8	5.01	6.7
8r	1	47	160-162	$C_{21}H_{18}N_2O_3$	Calcd.	72.8	5.24	8.1
			ethanol	(346.4)	Found	72.6	5.27	8.1
9	-	72	186-187	$C_{17}H_{14}N_4O_3$	Calcd.	63.4	4.38	17.4
			ethanol	(322.3)	Found	63.5	4.49	17.5
11	15	63	193-195	$C_{17}H_{14}N_4O_3$	Calcd.	63.4	4.38	17.4
			ethanol	(322.3)	Found	63.3	4.51	17.3

[a] Yields of purifield products are given

attached to the aniline have not to be protected and, therefore, the deprotection step can be eliminated.

The structure of **3b**, reported previously [7], has not been determined. On the other hand, during our previous studies X-ray structural analyses for **6** and **8** (Ar=4,6 dimethylpyrimidinyl-2) have been carried out, showing that both compounds exist in *Z*-form in the solid state regardless on the method of preparation[11,12]. On this basis, we assume that also compounds **8a-r** exist in the *Z*-form. This is supported by the observation that compounds **8** show in their ^{1}H-NMR spectra only one set of signals. The only exception is **8c**, for which two sets of signals indicate the equilibrium between *Z*- and *E*-form in the ratio 4:1 at room temp.

Compound **8o** was transformed by nitrosation with nitrous acid into the 3-heteroaryl substituted propenoate **9**, while by heating of 1H-benzotriazole (**10**) with **6** the isomeric compound **11** was isolated (Scheme 3). The structures of **9** and **11** were deduced from their ^{1}H-NMR spectra. **9** shows a typical ABCD spectrum for the aromatic protons of the 1-substituted benzotriazole, while for **11** two symmetrical multiplets characteristic for 2-substituted benzotriazoles were observed.

Table 2: ^{1}H-NMR Spectral Data

Compound	Solvent	δ (ppm) TMS int.stand., J(Hz)	
8a	DMSO-d_6		3.67 (s; 3H, COOMe), 6.70-7.40 (m; 4H, Ar). 7.40-7.60 (m; 5H, PhCO), 7.62 (d; 1H, CHNH), 9.30 (s) and 10.03 (s) (NHCO and OH), 9.96 (d, 1H, CHNH); J_{CHNH}= 13.4 Hz.
8b	DMSO-d_6		3.61 (s; 3H, COOMe), 6.70-6.99 (m; 4H, Ar), 7.40-7.65 (m; 5H, PhCO), 7.79 (d; 1H, CHNH), 7.90 (d; 1H, CHNH), 9.03 (s) and 9.09 (s) (NHCO, OH); J_{CHNH}= 14.0 Hz.
8c	$CDCl_3$	*Z* - Form:	3.85 (s; 3H, COOMe), 6.9-8.3 (m; 10 H, Ar, PhCO, NHCO), 7.88 (d; 1H, CHNH), 10.5 (br.d; 1H, CHNH); J_{CHNH}= 12.0 Hz.
		E - Form:	4.04 (s; 3H, COOMe), 9.1 (d; 1H, CHNH).
8d	$CDCl_3$		3.88 (s; 3H, COOMe), 7.2-7.95 (m; 10H, Ar, PhCO, CHNH), 8.35 (br.s; 1H, NHCO), 9.45 (br.d; 1H. CHNH); J_{CHNH}= 12.0 Hz.
8e	$CDCl_3$		3.90 (s; 3H, COOMe), 7.05-8.21 (m; 4H, -C_6H_4), 7.45-7.65 (m; 3H, PhCO), 7.79 (d; 1H, CHNH), 7.85-8.05 (m; 2H, PhCO), 8.4 (br.s; 1H, NHCO), 9.94 (br.d; 1H, CHNH); J_{CHNH}= 12.0 Hz.
8f	$CDCl_3$		3.93 (s; 3H, COOMe), 7.42 (d; 1H, H-6), 7.45-7.65 (m; 3H, PhCO), 7.78 (d; 1H, CHNH), 7.85-8.0 (m; 2H, PhCO), 8.19 (br.s; 1H, NHCO), 8.42 (dd; 1H, H-5), 9.17 (d; 1H, H-3), 11.08 (br.d, 1H. CHNH); $J_{H-5,H-6}$= 9.4 H $J_{H-3,H-5}$= 2.6 Hz, J_{CHNH}= 11.3 Hz.
8g	DMSO-d_6		2.31 (s; 3H, Me), 3.68 (s; 3H, COOMe), 7.45-7.65 (m; 6H, Ar, PhCO), 7.72 (d; 1H, CHNH), 7.95-8.10 (m; 2H, PhCO), 8.28 (d; 1H, CHNH), 9.37 (s; 1H, NHCO); J_{CHNH}= 12.3 Hz.
8h	DMSO-d_6		2.23 (s; 3H, Me), 3.66 (s; 3H, COOMe), 6.92-7.20 (m; 4H, Ar), 7.36 (d; 1H, CHNH), 7.45-7.60 (m; 3H, PhCO), 7.77-8.05 (m; 3H, PhCO and CHNH), 9.3 (s; 1H, NHCO), J_{CHNH}= 13 Hz.
8i	DMSO-d_6		2.28 (s; 3H, Me), 3.63 (s; 3H, COOMe), 6.70-7.30 (m; 4H, Ar), 7.40-7.65 (m; 3H, PhCO), 7.90 (d; 1H, CHNH), 7.95-8.15 (m; 2H, PhCO), 8.82 (d; 1H, CHNH), 9.1 (s; 1H, NHCO); J_{CHNH}= 13.0 Hz.
8j	DMSO-d_6		2.23 (s; 3H Me), 3.62 (s; 3H, COOMe), 7.08 (s; 4H, Ar), 7.45-7.60 (m; 3H, PhCO), 7.88 (d; 1H, CHNH), 8.08-8.15 (m; 2H, PhCO), 8.79 (d; 1H, CHNH), 9.1 (s; 1H, NHCO); J_{CHNH}= 13.0 Hz.
8k	DMSO-d_6		2.24 (s; 6H, 2xMe), 3.57 (s; 3H, COOMe), 7.05 (m; 3H, Ar), 7.28 (d; 1H, CHNH), 7.40-7.60 (m; 3H, PhCO), 7.85-8.2 (m; 3H, PhCO, CHNH), 9.0 (br.s; 1H, NHCO); J_{CHNH}= 13.0 Hz.
8l	DMSO-d_6		3.65 (s; 3H, COOMe), 7.40-8.05 (m; 9H, Ar, PhCO), 7.81 (d; 1H, CHNH), 9.09 (d; 1H, CHNH), 9.17 (s; 1H, NHCO); J_{CHNH}=14.0 Hz, (COOH exchanged).
8m	DMSO-d_6		3.66 (s; 3H, COOMe), 7.22-8.10 (m; 10H, Ar, PhCO, CHNH), 9.17 (d; 1H, CHNH), 9.23 (s; 1H, NHCO); J_{CHNH}= 11.5 Hz, (COOH exchanged).
8n	DMSO-d_6		1.30 (t, 3H, CH_2 Me), 3.67 (s; 3H, COOMe), 4.20 (q; 2H, CH_2Me), 7.28-8.28 (m; 10H, Ar, PhCO. CHNH), 9.21 (d; 1H, CHNH), 9.24 (s; 1H, NHCO); J_{CH_2Me}= 7.5 Hz, J_{CHNH}= 12.9 Hz.
8o	DMSO-d_6		3.61 (s; 3H, COOMe), 5.02 (s; 2H, NH_2), 6.5-7.0 (m; 4H, Ar), 7.35-8.80 (m; 7H, PhCO, CHNH, CHNH), 9.13 (br.s; 1H, NHCO).
8p	DMSO-d_6		3.70 (s; 3H, COOMe), 6.95-8.10 (m; 14H, Ar, PhCO), 8.18 (d; 1H, CHNH), 9.53 (s; 1H NHCO), 10.48 (d; 1H, CHNH); J_{CHNH}= 12.3 Hz.
8q	DMSO-d_6		3.64 (s; 3H, COOMe), 7.20-8.10 (m; 15H, Ar, PhCO, CHNH), 9.17 (s; 1H, NHCO), 9.09 (d; 1H, CHNH); J_{CHNH}= 12.6 Hz.
8r	DMSO-d_6		3.67 (s; 3H, COOMe), 7.22-8.24 (m; 12H, Ar, PhCO), 7.85 (d; 1H CHNH), 8.96 (d; 1H, CHNH), 9.34 (s; 1H, NHCO); J_{CHNH}= 12.6 Hz.
9	DMSO-d_6		3.85 (s; 3H, COOMe), 7.4-8.2 (m; 9H, Ar, PhCO), 8.32 (s; 1H, CH=C), 10.22 (s; 1H, NHCO).
11	DMSO-d_6		3.66 (s; 3H, COOMe), 7.31-7.48 (m; 5H, Ar, PhCO), 7.74-7.90 (m; 5H, Ar, PhCO, CH=C), 9.47 (s; 1H, NHCO).

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Experimental Part

Melting points: Kofler micro hot stage.- ^{1}H-NMR spectra: JEOL 90 Q FT spectrometer, TMS as int. standard.- Elemental analyses for C, H, and N: Perkin-Elmer CHN Analyser 240°C.- Methyl 2-benzoylamino-3-dimethylaminopropenoate was prepared according to lit.[10].

General procedure for the preparation of substituted methyl 2-benzoylamino-3-anilinopropenoates (**8**)

A mixture of **6** (2.48 g, 0.01 mole) and substituted anilines **7** (0.01 mole) in ethanol (5 ml) and conc. HCl (1 ml) was heated under reflux until all the starting material was consumed (1-25 h). The reaction was followed by TLC (DC Fertigplatten Kieselgel 60 F 254 with chloroform: methanol, 20:1). The volatile components were evaporated in vacuo and the solid residue recrystallized from an appropriate solvent to give **8a-r**. Experimental and analytical details: Tables 1 and 2.

Methyl 2-benzoyl-3-(benzotriazolyl-1)propenoate (**9**)

To a stirred ice-cold solution of **7 o** (108 mg, 0.001 mole) in water (3 ml) and conc. HCl (2 ml) a solution of $NaNO_2$ (100 mg) in water (2 ml) was added dropwise. Stirring was continued for additional 30 min. The solid, which precipitated during this time, was collected, washed with ice-cold water and recrystallized from ethanol to give **9**. Experimental and analytical data: Tables 1 and 2.

Methyl 2-benzoylamino-3-(benzotriazolyl-2)propenoate (**11**)

A mixture of 1H-benzotrizole (**10**; 286 mg, 0.002 mole) and **6** (496 mg, 0.002 mole) in ethanol (5 ml) and glacial acetic acid (1ml) was heated under reflux for 15 h. The solvents were evaporated in vacuo and the solid residue recrystallized from ethanol to give **11**. Experimental and analytical details: Tables 1 and 2.

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