A facile method for the synthesis of 3,1-benzooxazines from *N*-acyl-2-(alk-2-enyl)anilines

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Electrophilic addition of HCl or Br_2 to *N*-acyl-2-(alk-2-enyl)anilines is accompanied by intramolecular cyclization of these amides to give 3,1-benzooxazine hydrochlorides or hydrobromides in high yields.

Key words: *ortho*-alkenylanilines, *N*-acyl-2-(alk-1-enyl)anilines, hydrochlorination, heterocyclization, bromination, 3,1-benzooxazines.

Benzooxazines are often used in the synthesis of quinazolines[1—3] and organotellurium compounds.[4] Some 3,1-benzooxazines exhibit high biological activities and have been patented as cardiac stimulants;[5] they are used for the treatment of inflammatory processes[6] and as non-peptide oxytocin antagonists.[7] These compounds are usually synthesized from anthranilic acid derivatives or *o*-(α-hydroxy-, α-oxo- or α-haloalkyl)-substituted anilines.[8] Previously,[9,10] we reported that some *N*-acetyl-*o*-(cycloalk-1-enyl)anilines easily undergo heterocyclization on treatment with HCl or Br_2 to give 3,1-benzooxazines. This intramolecular cyclization serves as a convenient method for the synthesis of spiro-fused benzooxazines under mild conditions; we continued the research along this line. In this work, we studied the formation of 3,1-benzooxazines in the reaction with HCl or Br_2 as a function of the double bond geometry, the size of the ring in the alkenyl substituent, and the nature of the carboxylic acid residue in the initial *N*-acylaniline.

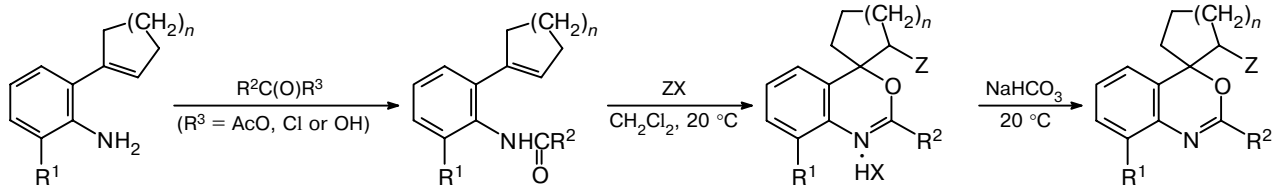
Results and Discussion

The reactions of amine **1**[9] with benzoyl, methacryloyl, and chloroacetyl chlorides resulted in *N*-benzoyl- (**2**), *N*-methacryloyl- (**3**), and *N*-chloroacetyl-2-(cyclopent-1-enyl)-6-methylanilines (**4**) in 90—92% yields (Scheme 1).

Formanilide **5** was prepared by heating arylamine **6**[10] in an excess of formic acid. The reaction of anilides **2** and **4** with gaseous HCl yielded 8-methyl-2-phenyl- (**7**) and 2-chloromethyl-8-methylspiro[4*H*-3,1-benzooxazine-4,1′-cyclopentane] hydrochlorides (**8**), and amides **5** and **9**[10] were converted into spiro[4*H*-3,1-benzooxazine-4,1′-cyclohexane] (**10**) and its 2-methyl analog **11** in high yields (see Scheme 1).

Hydrochlorination of amide **3** started with the addition of HCl at the double bond of the *N*-acyl residue giving rise to *N*-(3-chloro-2-methylpropanoyl)-6-(cyclopent-1-enyl)-2-methylaniline (**21**), which was then

Scheme 1



1, 6 **2—5, 9, 12** **7, 8, 10, 11, 13, 14** **15—20**

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
n	1	1	1	1	2	2	1	1	2	2	2	1	2	1	1	1	1	2	2	2
R^1	Me	Me	Me	Me	H	H	Me	Me	H	H	H	Me	H	Me	Me	Me	Me	H	H	H
R^2	—	Ph	CH_2=CMe	CH_2Cl	H	—	Ph	CH_2Cl	Me	H	Me	Me	H	Me	Ph	CH_2Cl	Me	H	Me	H
Z	—	—	—	—	—	—	H	H	—	H	H	—	Br	Br	H	H	Br	H	H	Br
X	—	—	—	—	—	—	Cl	Cl	—	Cl	Cl	—	Br	Br	—	—	—	—	—	—

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converted into 2-(1-chloropropan-2-yl)-8-methylspiro[4*H*-3,1-benzooxazine-4,1′-cyclopentane] hydrochloride (**22**) (Scheme 2).

The reactions of anilides **5** and **12** [9] with Br_2 in CCl_4 afforded spiro[4*H*-3,1-benzooxazine-4,1′-2-bromocyclohexane] hydrobromide (**13**) and 2,8-dimethylspiro[4*H*-3,1-benzooxazine-4,1′-2-bromocyclopentane] hydrobromide (**14**) in 95—97% yields (see Scheme 1). Treatment of the 3,1-benzooxazine hydrohalides **7**, **8**, **10**, **11**, **13**, and **14** with a 5% aqueous solution of $NaHCO_3$ furnished the corresponding bases **15—20**.

The structures of the compounds synthesized were proved by spectroscopy (Table 1—4) and elemental analysis (Table 5). The ^{1}H NMR spectrum of compound **21** exhibited only one signal for the olefinic proton H(2′) at δ 5.75, whereas the spectrum of the starting amide **3**

Scheme 2

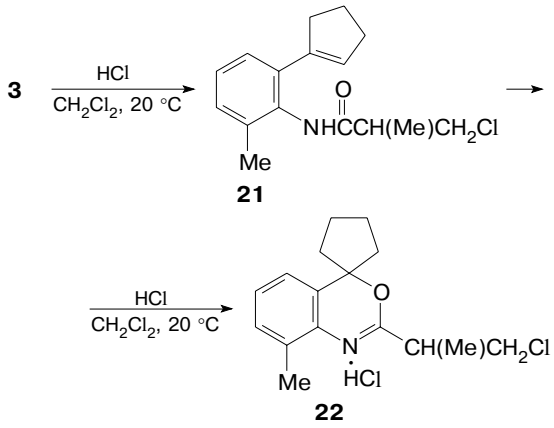


Table 1. ^{1}H NMR spectra of amines **24**, **25** and amides **2—5**, **21**, **26—28**

Compound	δ (*J*/Hz)			
	CH_3	H(2′)	CH_2 (m)	Other signals
2	2.16 (s)	6.05 (t, *J* = 2.0)	1.93—2.61	6.89—7.21 (m, 8 H, Ar); 7.22 (s, NH)
3	2.00, 2.20 (both s)	5.80 (t, *J* = 1.9)	5.40—5.77, 1.85—2.15	6.80—7.10 (m, 3 H, Ar); 7.45 (s, NH)
4	2.20 (s)	5.95 (t, *J* = 2.0)	1.90—4.70	6.83—7.11 (m, 3 H, Ar); 8.19 (s, NH)
5	—	5.70 (m)	1.55—2.20	7.00—8.10 (m, 8 H, Ar); 8.03 (s, CHO); 8.10 (s, NH)
21	1.02, 2.00 (both s)	5.75 (s)	1.70—3.60	2.70 (m, CH); 6.80—7.05 (m, 3 H, Ar); 8.05 (s, NH)
24	0.98 (t, *J* = 7.4); 2.01, 2.31 (both s)	5.62 (dt, *J* = 1.0, *J* = 7.1)	1.90	3.65 (s, 2 H, NH_2); 6.82 (d, H(3), *J* = 1.5); 6.94 (dd, H(5)); 6.68 (d, H(6), *J* = 7.9)
25	1.12 (t, *J* = 7.5); 2.01, 2.30 (both s)	5.54 (t, *J* = 7.0)	2.26	3.65 (s, 2 H, NH_2); 6.89 (s, H(3)); 6.93 (d, H(5)); 6.69 (d, H(6), *J* = 8.1)
26	0.89 (t, *J* = 7.5); 1.94, 2.11, 2.29 (all s)	5.65 (t, *J* = 8.0)	1.76	6.85 (s, H(3)); 7.04 (d, H(6), *J* = 8.3); 7.30 (s, NH); 8.14 (d, H(5))
27	1.07 (t, *J* = 7.5); 1.92, 2.10, 2.30 (all s)	5.43 (t, *J* = 8.2)	2.22	6.91 (s, H(3)); 7.02 (d, H(6), *J* = 6.9); 7.46 (s, NH); 8.01 (d, H(5))
28	0.90 (m, 2 CH_3); 1.90, 2.26, 2.30 (all s)	5.64 (t, *J* = 7.0)	1.30—1.75	6.81 (s, H(3)); 7.02 (d, H(6), *J* = 8.4); 7.34 (s, NH); 8.16 (d, H(6), *J* = 8.4)

Table 2. ^{13}C NMR spectra of compounds **2—5**, **21**, **24—28** ($CDCl_3$)

Compound	δ							
	C arom.	C(1′)	C(2′)	C=O	C(3′)	C(4′)	C(5′)	Other signals
2	126.2, 127.1, 128.7, 129.5, 130.0, 131.8, 132.3, 133.6, 134.3, 135.9	141.3	129.4	167.1	36.1	23.7	33.5	18.7 (CH_3)
3	119.9, 126.0, 126.8, 129.7, 132.2, 135.7, 136.3, 140.1	141.3	129.2	167.1	36.1	23.7	33.5	18.4, 18.8 (2 CH_3)
4	136.1, 128.3, 129.4, 127.5, 126.4, 131.2	140.9	130.2	165.0	36.2	23.8	33.6	18.4 (CH_3); 42.7 (CH_2Cl)
5	118.2, 121.0, 125.3, 128.0, 133.1, 135.0	129.5	127.3	152.2	24.7	21.7	22.7	29.7 (C(6′))
21	136.3, 132.1, 129.4, 126.7, 125.8, 129.8	128.8	140.8	172.2	33.3	23.4	36.1	15.9, 18.4 (2 CH_3); 43.5 (C(3″)); 45.8 (C(2″))
24	140.2, 128.1, 131.1, 127.9, 129.7, 115.1	133.1	129.2	—	24.6	14.2	—	20.5, 22.5 (2 CH_3)
25	140.4, 128.3, 127.2, 127.9, 129.3, 115.6	130.2	127.7	—	17.2	14.2	—	20.4, 21.6 (2 CH_3)
26	135.9, 132.1, 127.8, 131.4, 129.1, 120.2	132.2	128.5	167.9	25.0	14.0	—	20.7, 24.6, 22.4
27	135.7, 133.4, 127.6, 131.5, 127.7, 121.3	135.7	127.7	167.9	17.7	14.1	—	20.8, 21.6, 24.0
28	133.1, 132.2, 128.1, 131.4, 128.4, 120.1	132.3	131.6	171.1	25.0	14.0	—	13.6, 20.7, 22.1, 26.8, 27.7

Table 3. ^{1}H NMR spectra of hydrohalides (X = Cl or Br) of benzooxazines **7**, **8**, **10**, **11**, **13**, **14**, **22**, **31**, **32** and benzooxazines **15—20**, **30**, and **34** ($CDCl_3$)

Compound	δ (*J*/Hz)
7	1.80—2.70 (m, 4 CH_2); 2.55 (s, CH_3); 6.90—7.60 (m, 8 H, Ar); 11.20 (s, HCl)
8	1.90 (m, 4 CH_2); 2.53 (s, CH_3); 7.00 (m, 3 H, Ar); 9.90 (s, HCl)
10	1.30—2.40 (m, 5 CH_2); 7.00—7.40 (m, H(6), H(7)); 7.75 (d, H(8), *J* = 7.7); 9.08 (s, H(2)); 10.50 (s, HCl)
11	1.50—2.30 (m, 5 CH_2); 2.62 (s, CH_3); 7.68 (d, H(5), *J* = 7.2); 7.00—7.40 (m, H(6), H(7)); 7.90 (d, H(8), *J* = 7.6); 11.00 (s, HCl)
13	1.50—2.80 (m, 4 CH_2); 4.68 (s, H(2′)); 7.20—7.75 (m, 4 H, Ar); 9.40 (s, H(2)); 15.20 (s, HBr)
14	1.80—2.90 (m, 3 CH_2); 2.60 (s, CH_3); 3.00 (s, CH_3); 4.50 (s, H(2′)); 7.00—7.30 (m, 3 H, Ar); 13.40 (s, HBr)
15	1.80—2.70 (m, 4 CH_2); 2.60 (s, CH_3); 7.00—7.60 (m, 8 H, Ar)
16	1.90—2.50 (m, 4 CH_2); 2.13 (s, CH_3); 3.65 (s, CH_2Cl); 7.00 (m, 3 H, Ar)
17	1.90—2.70 (m, 3 CH_2); 2.12 (s, CH_3); 2.35 (s, CH_3); 4.33 (d.d, H(1′), *J* = 11.3, 2.3); 6.98—7.15 (m, 3 H, Ar)
18	1.50—2.30 (m, 5 CH_2); 6.50—7.30 (m, 4 H, Ar); 8.82 (s, H(2))
19	1.40—2.30 (m, 5 CH_2); 2.32 (s, CH_3); 7.17—7.40 (m, 4 H, Ar)
20	1.50—2.40 (m, 4 CH_2); 4.40 (s, H(2′)); 7.35 (s, H(2)); 7.00—7.30 (m, 4 H, Ar)
22	1.05 (d, CH_3); 2.50 (s, CH_3); 1.80—2.70 (m, 4 CH_2); 3.20—3.60 (m, CH_2Cl); 6.90—8.00 (m, 3 H, Ar); 11.00 (s, HCl)
30	0.85 (t, CH_3, *J* = 7.4); 0.95 (t, CH_3, *J* = 7.3); 1.52 (s, CH_3); 2.27 (s, CH_3); 1.20—2.23 (m, 5 CH_2); 6.76 (s, H(5)); 6.96 (m, H(7), H(8))
31	1.60—2.05 (m, CH_2); 1.00 (t, CH_3, *J* = 7.6); 1.91 (s, CH_3); 2.26 (s, CH_3); 2.62 (s, CH_3); 4.19 (d, H(1′), *J* = 10.6); 7.19 (s, H(5)); 7.62 (d, H(7)); 7.05 (d, H(8), *J* = 7.9); 15.15 (s, HBr)
32	1.40—1.90 (m, CH_2); 0.99 (t, CH_3, *J* = 6.6); 1.96 (s, CH_3); 2.31 (s, CH_3); 2.68 (s, CH_3); 4.12 (d, H(1′), *J* = 11.4); 6.94 (s, H(5)); 7.13 (d, H(8)); 7.71 (d, H(7), *J* = 8.0); 15.20 (s, HBr)
34	1.60—1.90 (m, CH_2); 1.02 (t, CH_3, *J* = 7.1); 1.83 (s, CH_3); 2.15 (s, CH_3); 2.33 (s, CH_3); 4.04 (d.d, H(1′), *J* = 11.3, 1.8); 6.85 (s, H(5)); 7.04 (d, H(8)); 7.09 (d, H(7), *J* = 8.0)

Table 4. ^{13}C NMR spectra of compounds **7**, **8**, **10**, **11**, **13—20**, **22** and **29—34** ($CDCl_3$)

Compound	δ								
	C(2)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)	Other signals
7	165.0	98.9	(119.6, 126.2, 127.9, 128.1, 128.3, 128.9, 129.2, 130.0, 131.1, 133.4)*						18.6 (CH_3); 23.8 (C(3′), C(4′)); 39.8 (C(2′), C(5′))
8	169.9	99.7	(122.6, 124.2, 127.8, 128.2, 131.2, 133.3)*						18.8 (CH_3); 23.2 (C(3′), C(4′)); 37.0 (C(2′), C(5′)); 46.8 (CH_2Cl)
10	159.6	89.8	132.8	127.8	118.6	129.8	124.2	139.8	20.5 (C(3′), C(5′)); 36.9 (C(2′), C(6′)); 21.5 (C(4′))
11	169.5	89.2	127.4	129.8	119.0	129.7	123.4	132.8	19.3 (CH_3); 20.5 (C(3′), C(5′)); 36.9 (C(2′), C(6′)); 24.0 (C(4′))
13	160.3	89.1	123.7	127.9	119.0	129.7	130.7	125.9	19.6 (C(5′)); 20.1 (C(4′)); 30.2 (C(3′)); 31.1 (C(6′)); 53.4 (C—Br)
14	172.5	97.4	121.0	128.9	132.8	124.0	126.0	127.9	19.5 (CH_3); 20.3 (C(4′); 20.6 (CH_3); 33.9 (C(5′); 35.1 (C(3′); 56.1 (C—Br)
15	155.7	88.9	(119.6, 126.2, 127.9, 128.1, 128.3, 128.9, 129.2, 130.0, 131.1, 137.7)*						18.7 (CH_3); 23.9 (C(3′), C(4′)); 39.9 (C(2′), C(5′))
16	163.0	90.4	(118.5, 126.2, 128.8, 128.4, 133.4, 137.6)*						18.3 (CH_3); 23.0 (C(3′), C(4′)); 36.7 (C(2′), C(5′))
17	159.4	90.4	123.7	123.4	125.8	130.9	131.6	136.2	17.5 (CH_3); 21.7 (C(4′)); 20.3 (CH_3); 33.8 (C(5′)); 34.5 (C(3′)); 56.7 (C(2′))
18	158.8	78.6	130.4	127.9	118.6	124.9	122.3	136.9	21.1 (C(3′), C(5′)); 21.7 (C(4′)); 36.4 (C(2′), C(6′))
19	159.5	78.4	130.4	128.0	122.0	126.0	123.7	136.1	20.8 (C(3′), C(5′)); 21.5 (CH_3); 24.2 (C(4′)); 36.0 (C(2′), C(6′))
20	150.0	78.9	128.3	124.0	126.4	129.0	128.1	135.9	20.0 (C(5′)); 19.3 (C(4′)); 30.0 (C(3′)); 29.5 (C(6′)); 53.8 (C(2′))
22	162.3	97.1	128.7	127.4	126.5	121.2	132.2	134.5	16.8, 23.8 (2 CH_3); 20.5 (C(3′), C(4′)); 39.9 (C(2′), C(5′)); 43.8 (C(3″)); 45.8 (C(2″))
29	170.6	89.8	127.8	123.5	123.6	128.9	123.5	139.1	12.4, 12.5, 20.4, 20.6 (4 CH_3); 15.8, 26.5, 28.4, 31.0, 43.1 (5 CH_2)
30	162.1	80.2	129.0	124.0	125.4	128.9	123.2	136.0	13.7, 14.1, 22.4, 27.8 (4 CH_3); 16.9, 28.3, 21.1, 35.2, 44.0 (5 CH_2)
31	168.8	90.0	121.6	117.8	124.3	131.0	125.2	140.5	12.7, 19.0, 21.4, 28.2 (4 CH_3); 26.3 (CH_2); 65.1 (C—Br)
32	168.5	90.7	124.0	118.3	124.2	130.5	124.4	140.5	12.5, 18.8, 21.3, 26.1 (4 CH_3); 24.9 (CH_2); 65.7 (C—Br)
33	159.8	81.8	125.9	124.6	135.5	129.9	124.2	136.3	13.3, 21.4, 21.5, 27.6 (4 CH_3); 26.4 (CH_2); 66.9 (C—Br)
34	159.8	81.6	126.3	124.8	135.7	130.1	124.1	136.3	13.3, 21.4, 23.5, 26.1 (4 CH_3); 26.1 (CH_2); 65.3 (C—Br)

* The signals related to C arom.

Table 5. Physicochemical characteristics and elemental analysis data for compounds **2—5**, **8—11**, **13—22**, and **24—34**

Compound	Yield (%)	B.p. (m.p.)/°C (p/Torr) or R_f (system)	Found / Calculated (%)				Molecular formula	IR spectrum, ν/cm^{-1}
			C	H	Br or Cl	N		
2	92	0.65 (*A*)	82.92 82.27	6.76 6.90	—	4.93 5.05	$C_{19}H_{19}NO$	3270 (NH)
3	90	0.67 (*A*)	79.56 79.63	7.45 7.94	—	5.70 5.80	$C_{16}H_{19}NO$	3280 (NH)
4	90	107	67.02 67.33	6.17 6.46	13.79 14.20	5.27 5.61	$C_{14}H_{16}ClNO$	3250 (NH)
5	74	0.37 (*A*)	77.48 77.58	7.27 7.51	—	6.71 6.96	$C_{13}H_{15}NO$	3280 (NH)
8	98	0.9 (*A*)	66.53 66.79	6.80 7.21	13.88 14.08	5.34 5.56	$C_{14}H_{18}ClNO$	—
9	97	105	58.29 58.75	5.82 5.99	24.65 24.77	4.61 4.90	$C_{14}H_{17}Cl_2NO$	—
10	94	0.18 (*A*)	65.41 65.68	6.52 6.78	14.65 14.91	5.77 5.89	$C_{13}H_{16}ClNO$	—
11	99	147	66.61 66.79	7.07 7.21	13.82 14.08	5.33 5.56	$C_{14}H_{18}ClNO$	—
13	97	0.20 (*A*)	42.95 43.24	3.80 4.19	43.98 44.26	3.55 3.88	$C_{13}H_{15}Br_2NO$	—
14	95	0.21 (*A*)	44.43 44.83	4.21 4.57	42.31 42.61	3.44 3.73	$C_{14}H_{17}Br_2NO$	—
15	97	0.90 (*A*)	81.96 82.28	6.42 6.91	—	4.78 5.05	$C_{19}H_{19}NO$	—
16	92	0.44 (*B*)	66.96 67.33	6.28 6.46	13.88 14.23	5.19 5.61	$C_{14}H_{16}ClNO$	—
17	96	0.37 (*B*)	57.14 57.16	5.44 5.48	27.21 27.16	4.76 4.76	$C_{14}H_{16}BrNO$	—
18	82	0.82 (*A*)	77.27 77.58	7.27 7.51	—	6.60 6.66	$C_{13}H_{15}NO$	—
19	93	0.88 (*B*)	78.02 78.10	7.78 7.96	—	6.45 6.51	$C_{14}H_{17}NO$	—
20	96	0.33 (*B*)	55.14 55.73	5.01 5.04	28.11 28.52	4.46 5.00	$C_{13}H_{14}BrNO$	—
21	70	0.66 (*A*)	68.78 69.17	7.15 7.26	12.52 12.76	4.78 5.04	$C_{16}H_{20}ClNO$	3293 (NH)
22	85	0.22 (*B*)	60.88 61.16	6.32 6.74	22.59 22.56	4.15 4.46	$C_{16}H_{21}Cl_2NO$	—
24	35	116 (3)	82.33 82.23	9.50 9.78	—	7.63 7.99	$C_{12}H_{17}N$	3380, 3460 (NH_2)
25	60	120 (3)	82.07 82.23	9.43 9.78	—	7.77 7.99	$C_{12}H_{17}N$	3380, 3460 (NH_2)
26	95	0.51 (*B*)	77.29 77.38	8.59 8.81	—	6.22 6.45	$C_{14}H_{19}NO$	3280 (NH)
27	94	0.4 (*B*)	77.29 77.38	8.36 8.81	—	6.28 6.45	$C_{14}H_{19}NO$	3280 (NH)
28	96	0.6 (*A*)	79.25 78.72	8.71 9.71	—	5.16 5.41	$C_{17}H_{25}NO$	3282 (NH)
29	93	0.36 (*A*)	67.78 69.02	8.47 8.86	11.72 11.98	4.31 4.73	$C_{17}H_{26}ClNO$	—
30	97	0.38 (*B*)	78.58 78.72	9.61 9.71	—	5.35 5.41	$C_{17}H_{25}NO$	—
31	98	0.23 (*A*)	44.38 44.59	5.08 5.08	42.19 42.38	3.39 3.71	$C_{14}H_{19}Br_2NO$	—
32	96	0.22 (*A*)	44.19 44.59	4.74 5.08	42.05 42.38	3.50 3.71	$C_{14}H_{19}Br_2NO$	—
33	96	0.42 (*B*)	56.50 56.77	5.89 6.13	26.41 26.68	4.70 4.73	$C_{14}H_{18}BrNO$	—
34	96	0.42 (*B*)	56.57 56.77	5.85 6.13	26.90 26.68	4.66 4.73	$C_{14}H_{18}BrNO$	—

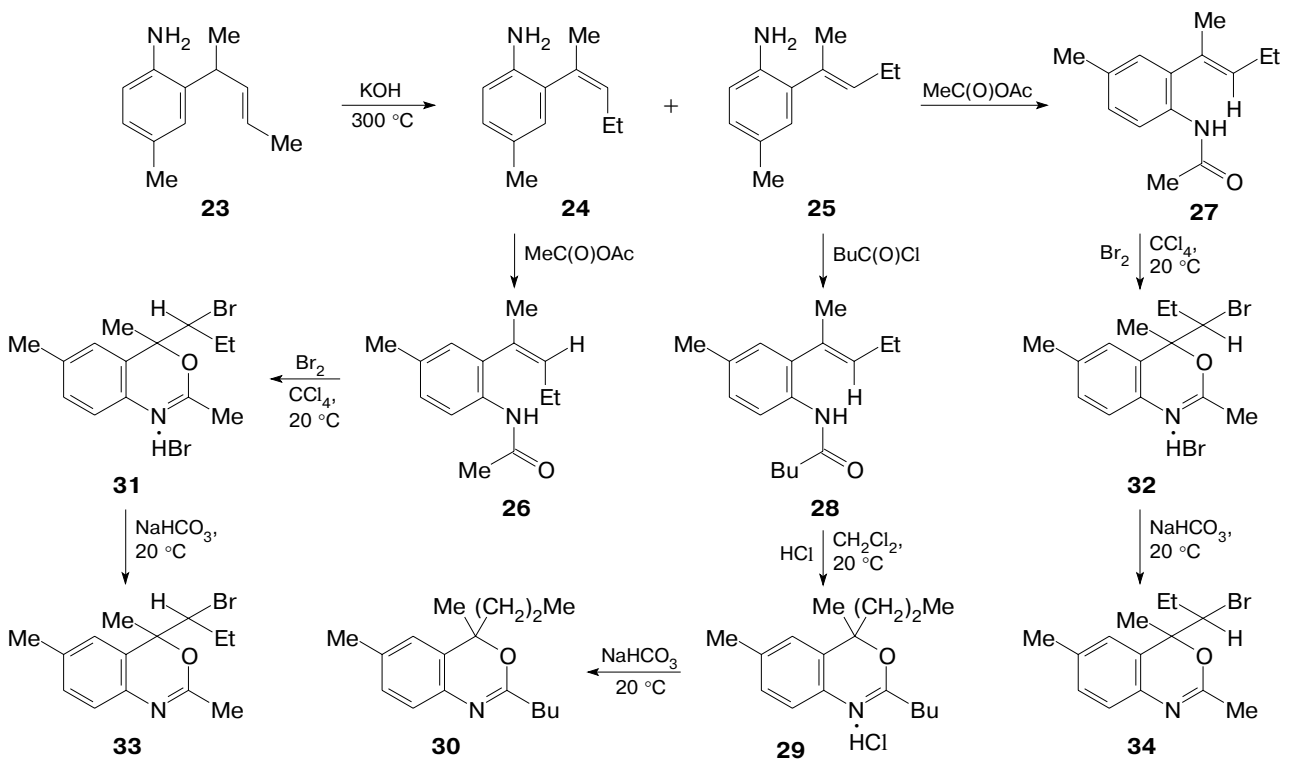
contained also signals for the protons of the terminal CH_2 groups at δ 5.40 and 5.77 (see Table 1). In the ^{13}C NMR spectrum of anilide **21**, signals for seven carbon atoms are present in the aliphatic region, three of them (δ 23, 33, and 36) belonging to the C atoms of the cyclopentene ring, as in the starting amide **3** (see Table 2). Common to all heterocycles is the signal corresponding to the spiro carbon atom C(4) observed in the δ 78—99 range of the ^{13}C NMR spectra, depending on the substituents R^2 and Z. In the spectra of hydrohalides **7**, **8** and **14**, this signal is shifted downfield by 9—10 ppm relative to its position in the spectra of bases **15—17** (see Table 4). An increase in the size of the ring spiro fused to the benzooxazine ring induces an upfield shift of this signal in hydrohalides **10**, **11**, and **13** (δ 88—89) and in the corresponding bases **18—20** (δ 78—79). The spectra of bromo derivatives **13**, **14**, **17**, and **20** contain a signal at δ 53—56 due to the C(2′) atom linked to the Br atom. The cyclization under consideration is an example of the known halocyclization[11] of *N*-acyl-*o*-alkenylarylamines; the Br and O atoms in the ring are apparently *trans*-oriented with respect to each other. The positions of signals of the aromatic and olefinic C atoms correspond to the chemical shifts calculated using additive parameters.[12]

In order to investigate the influence of the double bond geometry on the formation of benzooxazines, we prepared anilines with acyclic alkenyl substituents. Heating of 2-((*E*)-1-methylbut-2-enyl)-4-methylaniline (**23**)[13] with KOH at 300 °C yielded a mixture of 2-((*Z*)-1-methylbut-1-enyl)- (**24**) and 2-((*E*)-1-methylbut-1-enyl)-4-methylaniline (**25**) in ~2 : 1 ratio (Scheme 3), which were separated by vacuum distillation. When polyphosphoric acid was used in order to shift the double bond in molecule **23** toward the aromatic ring, the products with the indoline and indan structures were formed in addition to anilines **24** and **25**.[14] Acylation of arylamines **24** and **25** gave rise to amides **26—28**.

Passing of gaseous HCl through a solution of amide **28** in CH_2Cl_2 affords 2-butyl-4,6-dimethyl-4-propyl-3,1-benzooxazine hydrochloride (**29**), whose treatment with $NaHCO_3$ furnishes base **30**. The reaction of amide **26** or **27** with Br_2 in CCl_4 at 20 °C gives diastereomeric 4-(1-bromopropyl)-2,4,6-trimethyl-4*H*-3,1-benzooxazine hydrobromides **31** and **32**. The corresponding bases **33** and **34** were prepared by treating benzooxazines **31** and **32** with $NaHCO_3$ (see Scheme 3).

The structures of the resulting compounds **24—34** were also established by spectroscopy and using elemental analysis data (see Tables 1—5). The ^1H NMR signal for the olefinic proton H(2′) (see Table 1) in the spectrum of *trans*-alkenylaniline **25** is located in a lower field (δ 5.62) than in the spectrum of *cis*-isomer **24** (δ 5.54, Δδ = 0.08), which is in accord with the results of calculations by an additive scheme for olefins.[15] The signal of the methylene group in the *trans*-olefin **25** occurs in a lower field (δ 2.26) than the signal of the corresponding protons in *cis*-compound **24** (δ 1.90, Δδ = 0.36), because the anisotropy of the benzene ring has a deshielding effect in the former case and a shield-

Scheme 3



ing effect in the latter case. The ^{13}C NMR spectroscopy was also used to confirm either *cis*- or *trans*-configuration of the double bond. In the case of *trans*-configuration (compound **25**), the signals for the C atoms of the methyl group at C(1′) and of the methylene group shift upfield due to the 1,2-*syn*-interaction: δ 21.6 and 17.2 for compound **25** and δ 22.5 and 24.6 for compound **24** (see Table 2). The other signals are in accord with the values calculated using additive parameters.[16]

In the ^{13}C NMR spectra of α-bromopropyl-substituted benzooxazine hydrobromides **31** and **32**, the chemical shifts of the C atoms are different.

Thus, *N*-acylated *o*-(cyclopent-1-enyl)- and *o*-(cyclohex-1-enyl)anilines or *o*-((*E*)- and (*Z*)-1-methylbut-1-enyl)anilines react with HCl or Br_2 to give the corresponding 3,1-benzooxazine as the only product, irrespective of the geometry of the double bond, the size of the ring in the alkenyl group, and the nature of the carboxylic acid fragment in *N*-acylaniline.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300.13 and 75.47 MHz, respectively (Me_4Si was used as the internal standard), IR spectra were measured on a UR-20 spectrometer. The purity of the products was checked by GLC on a Chrom-5 chromatograph (SE-30 on Chromaton, a 1.2 m × 3.5 mm column, a flame ionization detector, 12 deg min^{-1}, helium as the carrier gas) and by TLC on Silufol UV-254 plates with CH_2Cl_2 (*A*) and CH_2Cl_2—MeOH, 95 : 5 (*B*) solvent systems.

Amines 24 and 25. The starting amine **23** [13] (40 mmol) was refluxed with solid KOH (150 mmol) at 300 °C for 1 h. After cooling the reaction mixture, the liquid was decanted from the solid KOH and distilled using a distillation column *in vacuo*.

Amides 26 and 27. Acetic anhydride (2.04 g, 20 mmol) was added to a solution of amine **24** or **25** (10 mmol) in 10 mL of CH_2Cl_2 and the mixture was left for 18 h. Then water was added to the reaction mixture, the aqueous layer was extracted with 100 mL of CH_2Cl_2, and the extract was washed with a 5% solution of $NaHCO_3$ until CO_2 evolution ceased and with water (20 mL) and dried with $MgSO_4$. The solvent was evaporated to give amide **26** or **27**.

Amides 2, 3, 4, and 28. Benzoyl, chloroacetyl, methacryloyl, or pentanoyl chloride (0.9 mmol) and K_2CO_3 (1.6 g, 12 mmol) were added with stirring at 20 °C to a solution of amine **1** [9], **6**,[10] or **24** (0.6 mmol) in 20 mL of dry CH_2Cl_2. The reaction mixture was stirred for 1.5 h with TLC monitoring. The precipitate was filtered off and washed with 10 mL of CH_2Cl_2. The filtrate was washed with water and a 10% solution of $NaHCO_3$ (2×25 mL), dried with $MgSO_4$, and concentrated *in vacuo*.

***N*-Formyl-2-(cyclohex-1-enyl)aniline (5).** Amine **6** (1 g, 5.8 mmol) was refluxed for 40 min in 10 mL of anhydrous formic acid and excess acid was evaporated *in vacuo*. The residue was twice dissolved in 5 mL of toluene with subsequent evaporation of the toluene *in vacuo* and recrystallized from hexane.

Anilide 21. Hydrogen chloride was passed for 10 min through a solution of amide **3** in CH_2Cl_2. The solvent was decanted from the resinous precipitate and evaporated *in vacuo* at 30 °C.

3,1-Benzooxazine hydrochlorides 7, 8, 10, 11, 22, and 29. Hydrogen chloride was passed through a solution of the corresponding anilide **2**, **4**, **5**, **9**,[10] **21**, or **28** (1 mmol) in 10 mL of CH_2Cl_2 until the initial amide disappeared (TLC). The solvent was evaporated *in vacuo* and the residue was dried *in vacuo*.

(α-Bromoalkyl)-3,1-benzooxazine hydrobromides 13, 14, 31, and 32. A solution of Br_2 (0.1 mL, 1.9 mmol) in 5 mL of CCl_4 was added dropwise with stirring to a solution of compound **5**, **12**,[9] **26**, or **27** (1.86 mmol) in 20 mL of dry CCl_4. The precipitate of the hydrobromide was filtered off and washed with 10 mL of CCl_4.

Preparation of 3,1-benzooxazines 15—20, 30, 33 and 34 (bases). The hydrohalide of the corresponding benzooxazine (5 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with 10 mL of a 5% solution of $NaHCO_3$. The organic phase was washed with water (10 mL), dried with $MgSO_4$, and concentrated *in vacuo*.

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