Synthesis of Indolones *via* Radical Cyclization of *N*-(2-Halogenoalkanoyl)-Substituted Anilines

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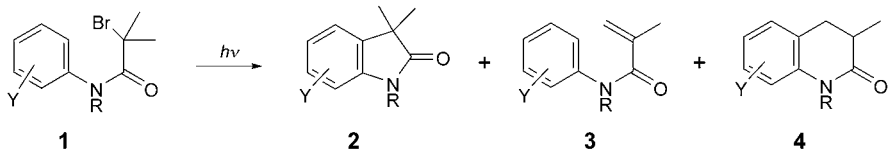
The radical reactions of *N*-(2-halogenoalkanoyl)-substituted anilines (anilides) of type **1** have been investigated under various conditions. Treatment of compounds **1a**–**1o** with Bu_3SnH in the presence of (2,2′-azobis(isobutyronitrile) (AIBN) afforded a mixture of the indolones (oxindoles) **2a**–**2o** and the reduction products **5a**–**5o** (*Table 1*). In contrast, the *N*-unsubstituted anilides **1p**–**1s**, **1u**, and **1v** gave the corresponding reduction products exclusively (*Table 1*). Similar results were obtained by treatment of **1** with Ni powder (*Table 2*) or wth Et_3B (*Table 3*). Anilides with longer *N*-(phenylalkyl) chains such as **6** and **7** were inert towards radical cyclization, with the exception of *N*-benzyl-2-bromo-*N*,2-dimethylpropanamide (**6b**), which, upon treatment with Ni powder in i-PrOH, afforded the cyclized product **9b** in low yield (*Table 4*). Upon irradiation, the extended anilides **6**, **7**, **10**, and **11** yielded the corresponding dehydrobromination products exclusively (*Table 5*).

Introduction. – Radical-induced cyclization reactions for the formation of N-containing heterocycles have attracted much attention from both synthetic and mechanistic points of view [1]. The indolones (oxindoles) are an important class of heterocycles not only due to various biological activities displayed by some members of this family, but also since these compounds are direct indole precursors [2][3]. The literature is replete with methods for the preparation of indolones [3][4]. Previously, we have demonstrated that *N*-(2-halogenoalkanoyl)-substituted aniline derivatives of type **1**, upon irradiation, afford the indolones **2**, along with the dehydrohalogenation products **3**, which underwent electrocyclic ring closure to the 'dihydrocarbostyrils', *i.e.*, 3,4-dihydroquinolin-2(1*H*)-ones, of type **4** (*Scheme 1*) [5a]. We have now examined the *radical* cyclization of **1** (and of related compounds) in the hope that this reaction might provide a facile route to indolones [6].

Scheme 1. *Light-Induced Cyclization or Dehydrobromination of* N-*Substituted 2-Bromo-2-methylpropanamides* **1**

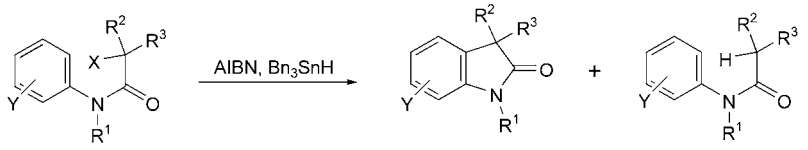


1 **2** **3** **4**

Results and Discussion. – When compounds **1a** and **1g**–**1o**, having electron-withdrawing or electron-donating substituents Y (= Cl, MeO, Me, acyl) in the *ortho*- or

para-positions of the aniline ring, were treated with Bu_3SnH and a small amount of 2,2′-azobis(isobutylonitrile) (AIBN) in boiling toluene, the 1-substituted 3,3-dimethylindolon-2-ones **2a** and **2g**–**2o**, respectively, were isolated in 34–80% yield as the main products, together with the 2-methylpropananilides **5a** and **5g**–**5o** (7–28%; *Table 1*). When the Y substituent of the aromatic ring was in *ortho*-position, as in the case of **1i**, **1k**, and **1m**–**1o**, the yields of the corresponding indolones **2** increased. When the *N*-(2-bromoalkanoyl) derivatives **1b** or **1e** were treated with Bu_3SnH and AIBN, then the reduction products **5b** and **5e**, respectively, were isolated in 73–75% yield, with the desired cyclization products **2b** and **2e** being present only as side products (8–17%). Treatment of compounds **1c** and **1d** and **1f** with Bu_3SnH and AIBN gave similar results; and reaction of the *N*-unsubstituted anilines **1p**–**1s**, and **1u** and **1v** afforded exclusively the reduction products **5p**–**5s**, and **5u** and **5v**, respectively (*Table 1*).

Table 1. *Tributyltin Hydride Promoted Reactions of Compounds* **1**. Bz = Benzoyl.



1 **2** **5**

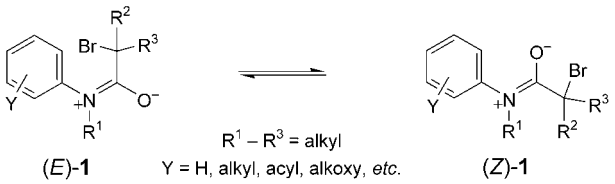
	Substituents					Isolated yield [%]	
	R^1	R^2	R^3	Y	X	**2**	**5**
1a	Ph	Me	Me	H	Br	39	13
1b	Ph	H	Me	H	Br	17	73
1c	Ph	H	Me	H	Cl	15	73
1d	Ph	H	Ph	H	Cl	10	70
1e	Ph	H	H	H	Br	8	75
1f	Ph	H	H	H	Cl	11	74
1g	Me	Me	Me	H	Br	48	22
1h	Me	Me	Me	*p*-Cl	Br	40	20
1i	Me	Me	Me	*o*-Cl	Br	34	12
1j	Me	Me	Me	*p*-MeO	Br	36	18
1k	Me	Me	Me	*o*-MeO	Br	38	12
1l	Me	Me	Me	*p*-Me	Br	38	24
1m	Me	Me	Me	*o*-Me	Br	50	28
1n	Me	Me	Me	*o*-Ac	Br	76	10
1o	Me	Me	Me	*o*-Bz	Br	80	7
1p	H	Me	Me	H	Br	–	78
1q	H	Me	Me	*o*-Ac	Br	–	61
1r	H	Me	Me	*o*-Bz	Br	–	73
1s	H	H	Me	H	Cl	–	82
1u	H	H	H	H	Br	–	81
1v	H	H	H	H	Cl	–	80

Owing to mesomerism, which confers to amide groups a partial double-bond character, the aromatic moieties and halogenoalkyl groups of the anilides **1a**–**1o** are probably mostly (*E*)-configured [5], whereas the *N*-unsubstituted anilides **1p**–**1s**, and **1u** and **1v** exist almost exclusively in the (*Z*)-form (*Scheme 2*), which is the disfavored

conformation for cyclization. This would explain why the above *N*-unsubstituted compounds ($R^1 = H$) did not cyclize, but underwent reduction.

The yields of the cyclized products **2b**–**2f** decreased as the degree of substitution at the α-C-atom of the 2-halogenoalkyl group in **1b**–**1f** decreased. The higher yields of the cyclized products **2a** and **2g**–**2o** relative to **2b**–**2f** might be attributed to differences in the stabilities of the intermediate carbamoyl radicals initially formed, the tertiary radicals being more stable than the secondary ones.

Scheme 2. *Representation of the Mesomeric Structures of Amides with (*E*)- vs. (*Z*)-Configured C=N Bonds.* For geometric reasons, only the *(E)*-isomers, with their (substituted) bromomethyl and aryl residues in close proximity, can cyclize.



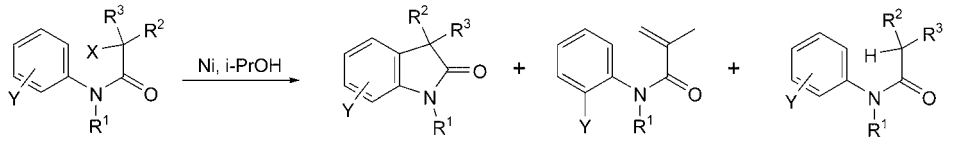
The above reaction could also be performed with Ni powder in i-PrOH instead of Bu_3SnH/AIBN, as tested for compounds **1a**–**1e**, **1g**–**1j**, **1l**–**1p**, **1t**, and **1u** (*Table 2*) [1h][6e]. The yields of the cyclized products **2a** and **2g** were not altered by additionally using AcOH in combination with Ni [7]. When the *ortho*-substituted substrates **1i**, **1m**, or **1n** were reacted, the corresponding dehydrobromination products **3i**, **3m**, and **3n**, respectively, were produced, along with the indolones **2i**, **2m**, and **2n**; the corresponding reduction products **5** were not detected in this case. The photochemical dehydrobromination of **1** to **3** has already been reported [5].

Triethylborane (Et_3B) has recently been used for the initiation of radical reactions to be carried out under mild conditions [1e][1g][8]. We, thus, also examined the radical reactions of compounds **1** with Et_3B in benzene or aqueous EtOH. Under these conditions, the indolones **2** and the reduction products **3** were also formed (*Table 3*), but the yields were generally lower than those obtained in the reactions with Bu_3SnH/AIBN or Ni powder.

The radical cyclization of the 2-bromo-2-methyl-*N*-(ω-phenylalkyl)-propanamides **6** or **7** to medium-membered lactams were unsuccessful. Treatment of **6** or **7** with Bu_3SnH/AIBN or with Et_3B gave the reduction products **8** as the sole products, except for the reaction of **6b** with Et_3B, in which 1,4-dihydro-2,4,4-trimethylisoquinolin-3(2*H*)-one (**9b**) was produced in low yield (14%) (*Table 4*).

Photochemical cyclizations of chloroacetamides to medium-membered lactams have been reported [9]. Irradiation of compounds **6**, **7**, **10**, or **11** (in O_2-free MeCN; *Pyrex* tube) with a high-pressure mercury lamp afforded only the dehydrobromination products **12**–**14** and **4**, respectively; the cyclized products (lactams) were not observed (*Table 5*). Irradiation of **6b** in the presence of a radical quencher, 2,6-di(*tert*-butyl)phenol, resulted in a decrease of the yield of **12b** (*Entry 3* in *Table 5*). Mechanistically, these dehydrobrominations can be rationalized by C–Br-bond homolysis, followed by elimination of HBr. The lack of cyclized products can be

Table 2. *Nickel Promoted Reactions of Compounds* **1**. Bz = Benzoyl.

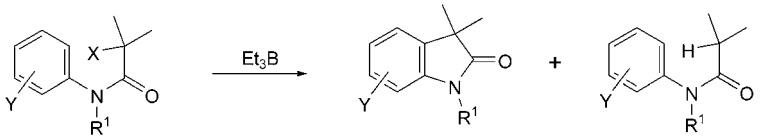


1 **2** **3** **5**

	Substituents					Isolated yield [%]		
	R^1	R^2	R^3	Y	X	**2**	**5**	**3**
1a	Ph	Me	Me	H	Br	69	12	–
1a[a])	Ph	Me	Me	H	Br	63	15	–
1b	Ph	H	Me	H	Br	11	14	–
1c	Ph	H	Me	H	Cl	trace	trace	–
1d	Ph	H	Ph	H	Cl	27	13	–
1e	Ph	H	H	H	Br	trace	50	–
1g	Me	Me	Me	H	Br	50	43	–
1g[a])	Me	Me	Me	H	Br	48	47	–
1h	Me	Me	Me	*p*-Cl	Br	48	45	–
1i	Me	Me	Me	*o*-Cl	Br	51	trace	48
1j	Me	Me	Me	*p*-MeO	Br	54	37	–
1l	Me	Me	Me	*p*-Me	Br	64	32	–
1m	Me	Me	Me	*o*-Me	Br	45	trace	31
1n	Me	Me	Me	*o*-Ac	Br	56	trace	27
1o	Me	Me	Me	*o*-Bz	Br	85	3	–
1p	H	Me	Me	H	Br	–	trace	–
1t	H	H	Ph	H	Cl	–	51	–
1u	H	H	H	H	Br	–	81	–

[a]) Reaction performed in the presence of AcOH.

Table 3. *Triethylborane Promoted Reactions of Compounds* **1**. Bz = Benzoyl.

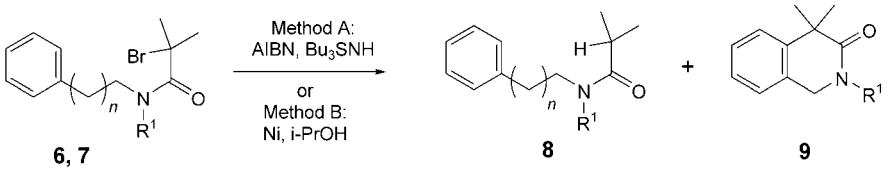


1 **2** **5**

	Substituents			Isolated yield (%)	
	R^1	Y	X	**2**	**5**
1a	Ph	H	Br	21	8
1a[a])	Ph	H	Br	43	20
1a[b])	Ph	H	Br	25	9
1g	Me	H	Br	27	13
1w[b])	Ph	H	I	38	26
1n	Me	*o*-Ac	Br	1	trace
1o	Me	*o*-Bz	Br	30	trace
1o[c])	Me	*o*-Bz	Br	13	trace
1x	Me	*o*-Bz	I	27	2

[a]) Reaction performed in the presence of Bu_3SnH (2.2 equiv.). [b]) 1.3 equiv. of Et_3B were used. [c]) EtOH/H_2O 3 : 1 was used as solvent.

Table 4. *Attempted Radical Cyclization with Elongated Amides*

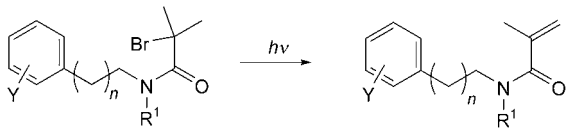


6, 7 **8** **9**

	Substituents			Isolated yield [%]	
	n	R^1	Method	**8**	**9**
6a	0	H	*A*	72	–
6a	0	H	*B*	–	–
6b	0	Me	*A*	45	–
6b	0	Me	*B*	50	14
7c	1	Me	*A*	48	–
7c	1	Me	*B*	43	–

attributed to an unfavorable conformation of the substrates (**6**, **7**, **10**, **11**), since there is no significant interaction between the aromatic ring and the 2-bromoalkyl group [5].

Table 5. *Attempted Photocyclization of Elongated Amides*



6, 7, 10, 11 **4, 12 – 14**

Entry		Substituents			Product	Isolated yield [%]
		n	R^1	Y		
1	**6a**	0	H	H	**12a**	12
2	**6b**	0	Me	H	**12b**	39
3	**6b**[a])	0	Me	H	**12b**	16
4	**6c**	0	Bn	H	**12c**	33
5	**6d**	0	Ph	H	**12d**	3
6	**6e**	0	H	3,4-OCH_2O–	**12e**	22
7	**7a**	1	H	H	**13a**	40
8	**7b**	1	H	3,4-$(MeO)_2$	**13b**	47
9	**10**	2	H	H	**14**	25
10	**11**	3	H	H	**4**	7

[a]) Reaction performed in the presence of 2,6-di-(*tert*-butyl)phenol (1 equiv.).

Experimental Part

General. Regular column chromatography (CC) and flash chromatography (FC) were performed with silica gel *Wakogel C-300* and *Merck 60*, resp. M.p.: *Yanaco MP-J3* micro-melting-point apparatus; uncorrected. B.p.: *Shibata GTO-350-RD* glass-tube-oven distillation apparatus. IR Spectra: *Jasco FT/IR-300* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Jeol JNM-EX-270* (270 MHz) or *Varian Gemini-200* (200 MHz) spectrometers; in $CDCl_3$, with Me_4Si as internal standard; δ in ppm, *J* in Hz.

General Procedure for Radical Reactions. Method A: To a soln. of **1** (1 mmol) in toluene (30 ml) was added dropwise a soln. of Bu_3SnH (1.1 equiv.) and AIBN (20 mg) in toluene (10 ml) over 2 h *via* syringe pump. The mixture was heated at reflux for 6 h. Then, more Bu_3SnH (1.1 equiv.) and AIBN (20 mg) in toluene (10 ml) were added dropwise over 1 h, and the mixture was refluxed for another 8 h. After evaporation of the solvent, AcOEt (20 ml) and 10% aq. KF soln. (50 ml) were added to the residue, and this mixture was stirred. The org. phase was separated, and the aq. phase was extracted with AcOEt. The combined org. phase was washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was subjected to CC (SiO_2; AcOEt/toluene 1:50 → 1:4) to afford the products **2** and **5** (see *Table 1*).

Method B: A soln. of **1** (1 mmol) and Ni powder (1.76 g, 30 mmol) in i-PrOH (15 ml) was heated at reflux under Ar gas for 20 h. The mixture was then cooled to r.t., diluted with AcOEt, and filtered through *Celite*. Then, H_2O was added to the filtrate, which was subsequently neutralized with sat. aq. $NaHCO_3$ soln., washed with H_2O, brine, dried ($MgSO_4$), and concentrated. The residual oil was subjected to CC (SiO_2; AcOEt/toluene 1:50 → 1:4) to afford the products **2**, **3**, and **5** (see *Table 2*).

Method C: To a soln. of **1** (1 mmol) in benzene (10 ml) was added dropwise a 1M soln. of Et_3B (0.6 molar equiv.) in THF *via* syringe pump. Then, the mixture was heated at reflux for 10 h. Usual workup gave the products **2** and **5** (see *Table 3*), which were identified by spectral comparison with literature data [5][6] and with authentic samples prepared independently from the corresponding anilines and alkanoyl or 2-methylprop-2-enoyl chlorides.

*7-Acetyl-1,3-dihydro-1,3,3-trimethylindol-2(2*H*)-one* (**2n**). B.p. 139–144°/3 Torr. IR (film): 1710, 1611. ^{1}H-NMR: 1.36 (*s*, 3 H); 2.34 (*s*, 6 H); 3.20 (*s*, 3 H); 7.12–7.30 (*m*, 3 H). Anal. calc. for $C_{13}H_{15}NO_2$ (217.26): C 71.86, H 6.96, N 6.45; found: C 71.68, H 7.14, N 6.32.

*7-Benzoyl-1,3-dihydro-1,3,3-trimethylindol-2(2*H*)-one* (**2o**). M.p. 175–176°. IR (KBr): 1718, 1660. ^{1}H-NMR: 1.43 (*s*, 6 H); 3.01 (*s*, 3 H); 7.07–7.64 (*m*, 7 H); 7.89–7.95 (*m*, 2 H). ^{13}C-NMR: 23.9; 29.2; 42.6; 120.7; 121.0; 123.5; 127.5; 127.7; 128.1; 129.9; 133.2; 136.8; 137.0; 140.7; 181.3; 195.0. Anal. calc. for $C_{18}H_{17}NO_2$ (279.32): C 77.39, H 6.13, N 5.01; found: C 77.25, H 6.23, N 4.80.

*1,4-Dihydro-2,4,4-trimethylisoquinolin-3(2*H*)-one* (**9b**) [10]. IR (film): 1659. ^{1}H-NMR: 1.50 (*s*, 6 H); 3.11 (*s*, 3 H); 4.59 (br. *s*, 2 H); 7.17–7.37 (*m*, 4 H).

Photoreactions of Homologous Amides (see *Table 5*). A soln. of one of the amides **6a**–**6e**, **7a**,**b**, **10**, or **11** (1 mmol) in MeCN (70 ml) was irradiated in a *Pyrex* tube with a high-pressure Hg lamp (500 W) under Ar gas for 10–15 h. After evaporation, the residue was subjected to CC (SiO_2; toluene/AcOEt 9:1 → 4:1) to yield the dehydrobrominated products **12a**–**12e**, **13a**, **13b**, **14**, or **4**, resp. Except for **12e** and **13b** (see below), these compounds were identified by comparison with authentic samples prepared independently from the corresponding amines and 2-methylprop-2-enoyl chloride.

N-*[(1,3-Benzodioxol-5-yl)methyl]-2-methylprop-2-enamide* (**12e**). M.p. 111–112°. IR (KBr): 3337, 3300, 1655, 1612. ^{1}H-NMR: 1.97 (*d*, *J* = 1.0, 3 H); 4.38 (*d*, *J* = 5.9, 2 H); 5.34 (br. *s*, 1 H); 5.70 (*s*, 1 H); 5.93 (*s*, 2 H); 6.17 (br. *s*, 1 H); 6.75–6.78 (*m*, 3 H). ^{13}C-NMR: 18.6; 43.5; 101.0; 108.2; 108.4; 119.6; 121.0; 132.1; 139.8; 146.9; 147.8; 168.1. Anal. calc. for $C_{12}H_{13}NO_3$ (219.23): C 65.74, H 5.98, N 6.39; found: C 65.76, H 6.01, N 6.35.

N-*[(3,4-Dimethoxyphenyl)ethyl]-2-methylprop-2-enamide* (**13b**). Oil. IR (film): 3332, 1656, 1616. ^{1}H-NMR: 1.92 (*d*, *J* = 0.7, 3 H); 2.80 (*t*, *J* = 6.6, 2 H); 3.51–3.58 (*m*, 2 H); 3.86 (*s*, 6 H); 5.29 (*d*, *J* = 1.3, 1 H); 5.62 (*s*, 1 H); 5.91 (br. *s*, 1 H); 6.72–6.83 (*m*, 3 H). ^{13}C-NMR: 18.5; 35.1; 40.8; 55.8; 111.3; 111.8; 119.3; 120.6; 131.3; 140.0; 147.6; 149.0; 168.4.

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