SIMPLE AND EFFICIENT SYNTHESIS OF 4*H*-3,1-BENZOXAZINES FROM 2-BROMOMETHYLPHENYL ISOCYANATE AND AMINES

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Dedicated to Professor Pavol Kristián on the occasion of his 60th birthday.

Reaction of 2-bromomethylphenyl isocyanate (*II*; prepared by radical bromination of 2-tolyl isocyanate with N-bromosuccinimide) with aliphatic and aromatic amines takes place on the NCO group under formation of stable N-alkyl(aryl)-N′-(2-bromomethylphenyl)ureas *III*. On treatment with sodium hydrogen carbonate in water or sodium hydride in N,N-dimethylformamide, the ureas *III* are cyclized to give 2-alkyl(aryl)amino-4*H*-3,1-benzoxazines *IV* in good yields. Reaction of isocyanate *II* with alcohols leads to alkyl 2-bromomethylphenyl carbamates. Structure of the synthesized compounds has been proven by spectral methods and elemental analysis.

In our previous papers[1-4] we studied the synthesis and reactions of 2-bromomethylphenyl isothiocyanate (*I*) in regard to the selective reaction of its reaction centers (the bromine atom and the NCS group) with nucleophilic reagents, The synthetic utilization of isothiocyanates with reactive halogen atom in the preparation of heterocyclic compounds is well known[5-8]. Less attention, however, has been paid to analogous reactions of the corresponding halogeno isocyanates[9,10].

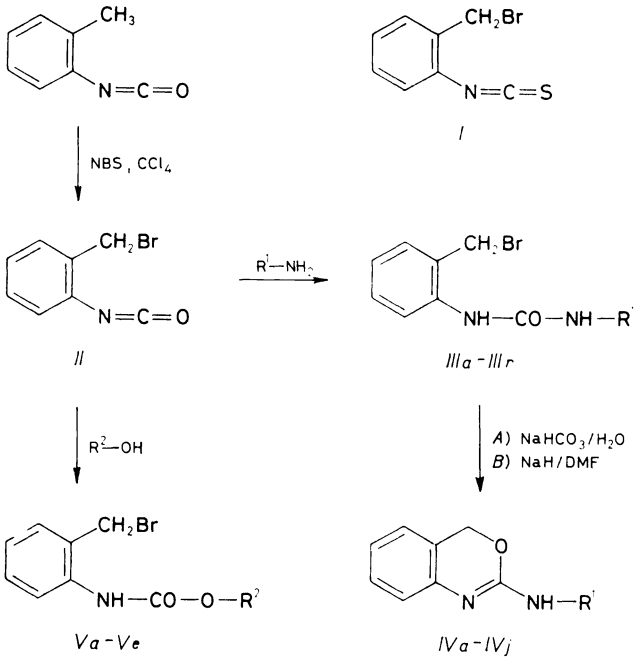
The present work is aimed at the synthesis of 2-alkyl-(aryl)amino-4*H*-3,1-benzoxazines *IV* from 2-bromomethylphenyl isocyanate (*II*) (which is more reactive than the 2-chloromethyl derivative) and a set of primary aliphatic or aromatic amines.

4*H*-3,1-Benzoxazines are tranquilizers and exhibit strong anxiolytic effects: two known compounds of this type, ethyfoxin[11] and brofoxin[12], may be mentioned.

Traditional approaches to 4*H*-3,1-benzoxazines use cyclization of N-acylaminobenzyl alcohols[13] and N-aryl-N′-(2-hydroxymethylphenyl)ureas[14] with concentrated hydrobromic acid. These compounds can also be prepared by reaction of 2-aminobenzyl halides with glacial acetic acid[14]. Other routes leading to 4*H*-3,1--benzoxazines make use of condensation reactions of 2-aminobenzyl alcohols with aldehydes[15] or cyclization of N,N-dialkyl-N′-(2-chloromethylphenyl)ureas, prepared from 2-chloromethyl isocyanates and dialkylanilines[16].

2-Bromomethylphenyl isocyanate (*II*) was prepared in 78% yield by radical bromination of 2-tolyl isocyanate with N-bromosuccinimide in the presence of di-

benzoyl peroxide (Scheme 1). The IR spectrum of compound *II* exhibits a characteristic absorption band of ν(NCO) at 2 280 cm^{-1}, its ^1H NMR spectrum shows a methylene singlet at δ 4·42 and signals of aromatic protons in the region δ 7·00 to 7·21.



For R^1 see Table I, for R^2 Table V

SCHEME 1

We treated compound *II* with a series of aliphatic and aromatic amines. The reaction took place on the NCO group under formation of stable N-alkyl(aryl)-N'-(2-bromomethylphenyl)ureas *IIIa*–*IIIr* (Scheme 1, Tables I and II). The obtained ureas *IIIa*–*IIIj* were then cyclized by reaction with sodium hydrogen carbonate in water (Method *A*) or with sodium hydride in N,N-dimethylformamide (Method *B*) to give 2-alkyl(aryl)amino-4*H*-3,1-benzoxazines *IVa*–*IVj* (Scheme 1, Table III). Infrared spectra of compounds *IV* exhibit characteristic absorption bands at 3 425 cm^{-1} due to the N—H vibrations and a strong C=N band at 1 620 to 1 630 cm^{-1}. Their ^1H NMR spectra display signals of the oxazine methylene group at δ 5·05–5·18 (Table IV). The chemical shift of the C-2 carbon signal in ^{13}C NMR spectrum of compound *IVd* (δ 155·5) indicates the presence of the oxazine ring.

TABLE I

N-Alkyl(aryl)-N'-(2-bromomethylphenyl)ureas *IIIa*—*IIIr*

Product R^1	Formula (M.w.)	Yield, % (M.p., °C)	Calculated/Found		
			% C	% H	% N
IIIa	$C_{10}H_{13}BrN_2O$	91	46·71	5·09	10·89
CH_3CH_2	(257·1)	(74—76)	46·70	5·11	10·88
IIIb	$C_{12}H_{17}BrN_2O$	76	50·54	6·00	9·82
$CH_3(CH_2)_3$	(285·2)	(84—85)[a]	50·53	6·01	9·83
IIIc	$C_{12}H_{17}BrN_2O$	74	50·54	6·00	9·82
$(CH_3)_2CHCH_2$	(285·2)	(78—79)[a]	50·55	6·05	9·80
IIId	$C_{13}H_{19}BrN_2O$	77	52·18	6·40	9·36
$CH_3(CH_2)_4$	(299·2)	(70)	52·16	6·42	9·34
IIIe	$C_{14}H_{21}BrN_2O$	57	53·68	6·57	8·94
$CH_3(CH_2)_5$	(313·2)	(72—73)[a]	53·66	6·56	8·93
IIIf	$C_{15}H_{23}BrN_2O$	68	55·05	7·08	8·55
$CH_3(CH_2)_6$	(327·3)	(74)	55·07	7·07	8·56
IIIg	$C_{16}H_{17}BrN_2O$	81	57·67	5·14	8·40
$C_6H_5CH_2CH_2$	(333·2)	(105)	57·69	5·15	8·40
IIIh	$C_{15}H_{15}BrN_2O$	88	56·44	4·73	8·77
$C_6H_5CH_2$	(319·2)	(107)	56·45	4·75	8·79
IIIi	$C_{14}H_{13}BrN_2O$	80	55·10	4·29	9·17
C_6H_5	(305·2)	(140)[a]	55·12	4·27	9·19
IIIj	$C_{14}H_{12}BrClN_2O$	87	49·51	3·56	8·29
4-ClC_6H_4	(339·6)	(137)	45·53	3·58	8·31
IIIk	$C_{15}H_{15}BrN_2O$	82	56·44	4·73	8·77
4-$CH_3C_6H_4$	(319·2)	(156)	56·46	4·75	8·79
IIIf	$C_{15}H_{15}BrN_2O\alpha$	78	53·74	4·51	8·35
4-$CH_3OC_6H_4$	(335·2)	(151)	53·72	4·52	8·33
IIIm	$C_{14}H_{12}BrN_2O$	82	43·78	3·14	7·29
4-BrC_6H_4	(384·1)	(149)	43·77	3·16	7·31
IIIn	$C_{14}H_{12}BrClN_2O$	84	49·51	3·56	8·29
3-ClC_6H_4	(339·6)	(156)	49·52	3·54	8·28
IIIo	$C_{15}H_{14}BrClN_2O$	71	50·94	3·99	7·92
2-CH_3-4-ClC_6H_3	(353·6)	(159)	50·94	4·01	7·95
IIIp	$C_{24}H_{19}BrN_2O$	75	66·83	4·44	6·49
1-naphthyl	(431·3)	(143)	66·81	4·50	6·51
IIIr	$C_{11}H_{15}BrN_2O$	93	48·72	5·57	10·33
$(CH_3)_2CH$	(271·2)	(92)	48·71	5·58	10·32

[a] Decomposition.

TABLE II

Spectral data of N-alkyl(aryl)-N'-(2-bromomethylphenyl)ureas *IIIa*—*IIIr*

Compound	IR, cm^{-1} [a]		^1H NMR, δ in ppm [b]			
	ν(NH)	ν(CO)	CH_2	H-arom.	NH	Other signals
IIIa	3 340, 3 277	1 635	5·80	7·32—7·81	8·67 12·25	1·41 t, 3 H (CH_3) 3·47—3·85 m, (CH_2N)
IIIb	3 348, 3 295	1 580	5·53	7·05—7·42	9·43 11·98	0·96 t, 3 H (CH_3) 1·25—1·80 m, 4 H (CH_2) 3·27—3·53 m, 2 H (CH_2N)
IIIc	3 327, 3 265	1 677	5·50	7·02—7·27	9·45 12·05	0·97 d, 6 H (CH_3) 1·7—2·0 m, 1 H (CH) 3·21 dd, 2 H (CH_2N)
IIId	3 165, 3110	1 667	5·53	7·07—7·51	9·40 11·96	0·86 t, 3 H (CH_3) 1·21—1·72 m, 6 H (CH_2) 3·25—3·50 m, 2 H (CH_2N)
IIIe	3 165, 3 110	1 670	5·49	7·02—7·35	9·45 12·05	0·85 t, 3 H (CH_3) 1·15—1·80 m, 8 H (CH_2) 3·23—3·47 m, 2 H (CH_2)
IIIf	3 320	1 680	5·82	7·38—7·80	12·05 10·21	1·07 t, 3 H (CH_3) 1·50 m, 10 H (CH_2) 3·67 m, 2 H (CH_2N)
IIIg	3 345, 3 165 3 115	1 667	5·87	7·30—7·72	10·60 12·27	3·92 t, 2 H (CH_2) 4·77 m, 2 H (CH_2N)
IIIh	3 330, 3 296 3 275	1 635	5·87	7·35—7·82	10·65 12·32	4·87 s, 2 H (CH_2N)
IIIi	3 295	1 635	5·95	7·10—8·16	8·64 9·67	
IIIj	3 280	1 635	5·02	7·15—8·10	8·57 9·80	
IIIk	3 285	1 640	5·08	7·10—8·17	8·60 9·60	2·56 s, 3 H (CH_3)

TABLE II
(*Continued*)

Compound	IR, cm^{-1} [a]		^1H NMR, δ in ppm [b]			
	ν(NH)	ν(CO)	CH_2	H-arom.	NH	Other signals
IIIl	3 290	1 635	5·10	7·05—8·07	8·60	3·90 s, 3 H (CH_3)
IIIm	3 275	1 633	5·05	7·27—8·12	8·57 9·75	
IIIn	3 287	1 635	4·95	7·00—7·93	8·00 9·19	
IIIo	3 278	1 635	4·98	7·00—7·90	8·40	2·31 s, 3 H (CH_3)
IIIp	3 273	1 635	5·13	7·27—8·60	8·97 9·55	
IIIr	3 315, 3 298 3 276	1 627	5·81	7·37—7·80	10·17 11·91	1·47 d, 6 H (CH_3) 4·42 m, 1 H (CHN)

[a] Compounds *IIIa—IIIc*, *IIIf—IIIh* and *IIIr* were measured in $CHCl_3$, *IIId*, *IIIe* and *IIIi—IIIp* in KBr; [b] measured in a mixture $CDCl_3$–$(CD_3)_2SO$ (5 : 1).

The assumed structure is also confirmed by mass spectra of selected derivatives (Table IV).

Alcohols react analogously with 2-bromomethylphenyl isocyanate under formation of alkyl 2-(bromomethylphenyl)carbamates *V* (Scheme 1, Table V). The structure of these products was confirmed by spectral methods and elemental analysis (Table VI).

EXPERIMENTAL

Infrared spectra were measured in chloroform or in KBr pellets on an IR 75 (Zeiss, Jena) instrument; wavenumbers are given in cm^{-1}. Proton and ^{13}C NMR spectra were taken on a TESLA BS 497 (80 MHz, for H^1) and TESLA BS 567 spectrometer (25·04 MHz, for ^{13}C). Chemical shifts are given in ppm (δ-scale) and coupling constants (J) in Hz. Signals in the ^{13}C NMR spectra were assigned by the selective proton decoupling method. Mass spectra were obtained with an MS 902 S (AEI Manchester) instrument at 70 eV.

2-Bromomethylphenyl Isocyanate (*II*)

A mixture of 2-tolyl isocyanate (13·3 g, 0·1 mol), N-bromosuccinimide (17·8 g, 0·1 mol), dibenzoyl peroxide (1·24 g, 0·05 mol) and tetrachloromethane (20 ml) was refluxed for 30 min. After cooling, the separated succinimide was filtered off, washed with tetrachloromethane and

the solvent was evaporated. The residue was dissolved in small amount of hexane and set aside at −18°C overnight. The crystalline 2-bromomethylphenyl isocyanate was collected on filter and crystallized from hexane; m.p. 8–12°C, yield 78%. For C_8H_6BrNO (211·9) calculated: 45·30% C, 2·83% H, 6·60% N; found: 45·33% C, 2·81% H, 6·58% N. IR spectrum ($CHCl_3$): 2 280 (NCO). ^{1}H NMR spectrum ($CDCl_3$): 4·42 s, 2 H (CH_2); 7·00–7·21 m, 4 H (H-arom.).

N-Alkyl(aryl)-N′-(2-bromomethylphenyl)ureas *IIIa–IIIr*

A solution of the amine (10 mmol) in dry ether (40 ml) was added at 0°C to a solution of 2-bromomethylphenyl isocyanate (*II*, 2·12 g, 10 mmol) in dry ether (20 ml). After standing for 1 h, the mixture was diluted with hexane (50 ml) and the precipitate was filtered and dried. The yields and physicochemical characteristics are given in Table I, the spectral data in Table II.

TABLE III

2-Alkyl(aryl)amino-4*H*-3,1-benzoxazines *IVa–IVj*

Product R[1]	Formula (M.w.)	M.p., °C Solvent	Yield %	Calculated/Found		
				% C	% H	% N
IVa	$C_{10}H_{12}N_2O$	93[a]	65[d]	68·16	6·86	15·89
CH_3CH_2	(176·2)	hexane		68·14	6·88	15·90
IVb	$C_{12}H_{16}N_2O$	87–88[b]	58[d]	70·56	7·89	13·71
$CH_3(CH_2)_3$	(204·3)	hexane		70·57	7·90	13·73
IVc	$C_{12}H_{16}N_2O$	106–107	66[d]	70·56	7·89	13·71
$(CH_3)_2CHCH_2$	(204·3)	hexane		70·53	7·92	13·73
IVd	$C_{13}H_{18}N_2O$	73–74	54[d]	71·52	8·31	12·83
$CH_3(CH_2)_4$	(218·3)	hexane		71·53	8·29	12·85
IVe	$C_{14}H_{20}N_2O$	67	46[d]	72·37	8·67	12·05
$CH_3(CH_2)_5$	(232·3)	LP[g]		72·38	8·69	12·07
IVf	$C_{15}H_{22}N_2O$	55	76[e]	73·13	9·00	11·37
$CH_3(CH_2)_6$	(246·4)	LP[g]		73·11	9·03	11·39
IVg	$C_{16}H_{16}N_2O$	92–93	68[e]	76·16	6·39	11·10
$C_6H_5CH_2CH_2$	(252·3)	ethanol		76·14	6·41	11·13
IVh	$C_{15}H_{14}N_2O$	143–145[f]	55[e]	75·60	5·95	11·75
$C_6H_5CH_2$	(238·3)	ethanol		75·58	5·85	11·72
IVi	$C_{14}H_{12}N_2O$	146[c]	69[e]	74·98	5·39	12·49
C_6H_5	(224·3)	ethanol		75·00	5·37	12·51
IVj	$C_{14}H_{11}ClN_2O$	144–146	53[e]	65·00	4·29	10·83
4-ClC_6H_4	(258·7)	ethanol		65·01	4·28	10·84

[a] M.p. 94–95°C (ethanol, ref.[14]); [b] m.p. 91–92°C (ref.[16]); [c] m.p. 145–146°C (ref.[16]); [d] method *A*; [e] method *B*; [f] m.p. 125–126°C (ref.[16]); [g] LP light petroleum.

N-Alkyl(aryl)amino-4*H*-3,1-benzoxazines *IVa*—*IVj*

A) A solution of sodium hydrogen carbonate (1·68 g, 20 mmol) in water (50 ml) was added to a suspension of the urea *IIIa*—*IIIe* (10 mmol) in water (30 ml) and the mixture was refluxed

TABLE IV

Spectral data of 2-alkyl(aryl)amino-4*H*-3,1-benzoxazines *IVa*—*IVj*

Compound	IR (cm^{-1}), $CHCl_3$		^1H NMR (δ in ppm), $CDCl_3$			Other signals
	ν(NH)	ν(C=N)	CH_2	NH	H-arom.	
IVa[a]	3 447	1 620	5·05	4·67	6·83—7·17	1·12 t, 3 H (CH_3) 3·28 q 2 H (CH_2)
IVb[b]	3 447	1 625	5·07	4·25	6·85—7·21	0·95 t, 3 H (CH_3) 1·19—1·67 m, 4 H (CH_2) 3·27 t, 2 H (CH_2N)
IVc[c,e]	3 450	1 627	5·05	4·30	6·82—7·17	0·87 d, 6 H (CH_3) 1·60—1·92 m, 1 H (CH) 3·07 d, 2 H (CH_2N)
IVd[d]	3 450	1 625	5·08	4·31	6·87—7·22	0·88 t, 3 H (CH_3) 1·15—1·62 m, 6 H (CH_2) 3·28 t, 2 H (CH_2N)
IVe	3 447	1 620	5·10	4·65	6·88—7·23	0·86 t, 3 H (CH_3) 1·07—1·62 m, 8 H (CH_2) 3·27 t, 2 H (CH_2N)
IVf	3 300	1 620	4·06	—	6·85—7·20	0·84 t, 3 H (CH_3) 1·25 m, 10 H (CH_2) 3·26 t, 2 H (CH_2N)
IVg	3 445	1 627	5·05	—	6·89—7·30	2·87 t, 2 H (CH_2) 3·59 t, 2 H (CH_2N)
IVh	3 442	1 625	5·12	4·25	6·90—7·95	4·50 s, 2 H (CH_2N)
IVi	3 427	1 630	5·18	—	6·96—7·62	—
IVj	3 425	1 627	5·18	—	7·00—7·58	—

[a] Mass spectrum, *m/z* (relat. intens., %): 176 (M^+, 83), 148 (34), 132 (63), 105 (50), 104 (33), 78 (31), 77 (28), 51 (13), 44 (100), 29 (13). [b] Mass spectrum, *m/z* (relat. intens., %): 204 (M^+, 100), 162 (26), 148 (100), 106 (30), 105 (60), 104 (39), 78 (26), 77 (34), 72 (18). [c] Mass spectrum, *m/z* (relat. intens., %): 204 (M^+, 29), 148 (100), 132 (64), 106 (12), 105 (32), 104 (16), 78 (13), 77 (17), 72 (9). [d] Mass spectrum, *m/z* (relat. intens., %): 218 (M^+, 70), 203 (10), 189 (17), 176 (13), 162 (38), 148 (100) 132 (98), 105 (70), 104 (43), 78 (33), 77 (53). [e] ^{13}C NMR spectrum, ($CDCl_3$): 155·5 (C-2); 67·4 (C-4); 128·8, 123·4, 121·9, 121·5 (C-5, C-6, C-7, C-8); 142·9 (C-9); 120·9 (C-10); 48·9 (CH_2N); 28·6 (CH); 20·0 (CH_3).

TABLE V

Alkyl 2-(bromomethyl)phenylcarbamates *Va*— *Ve*

Product R^2	Formula (M.w.)	Yield, % (M.p., °C)[a]	Calculated/Found		
			% C	% H	% N
Va	$C_9H_{10}BrNO_2$	88	44·28	4·12	5·73
CH_3	(244·1)	(130)	44·27	4·11	5·75
Vb	$C_{10}H_{12}BrNO_2$	89	46·53	4·68	5·42
CH_3CH_2	(258·1)	(116)	46·54	4·76	5·44
Vc	$C_{12}H_{16}BrNO_2$	87	50·36	5·63	4·89
$CH_3(CH_2)_3$	(286·2)	(88)	50·34	5·61	4·92
Vd	$C_{12}H_{16}BrNO_2$	85	50·36	5·63	4·89
$CH_3CH_2(CH_3)CH$	(286·2)	(89)	50·37	5·65	4·91
Ve	$C_{12}H_{16}BrNO_2$	88	50·36	5·63	4·89
$(CH_3)_2CHCH_2$	(286·2)	(91)	50·35	5·63	4·91

[a] Crystallized from ethanol.

TABLE VI

Spectral data of alkyl 2-(bromomethyl)phenylcarbamates *Va*— *Ve*

Compound	IR, cm^{-1}[a]			^1H NMR, δ in ppm[b]			
	ν(NH)	ν(C—O—C)	ν(CO)	CH_2	NH	H-arom.	Other signals
Va	3 280	1 260	1 690	4·47	6·85	6·95—7·87	3·80 s, 3 H (CH_3O)
Vb	3 400	1 292	1 725	4·46	6·81	6·95—7·86	1·30 t, 3 H (CH_3) 4·22 q, 2 H (CH_2O)
Vc	3 400	1 295	1 724	4·46	6·81	6·92—7·86	0·94 t, 3 H (CH_3) 1·17—1·75 m, 4 H (CH_2) 4·16 t, 2 H (CH_2L)
Vd	3 403	1 290	1 723	4·45	6·75	7·06—7·85	0·91 t, 3 H (CH_3) 1·25 d, 3 H (CH_3) 1·43—1·70 m, 2 H (CH_2) 4·72—4·95 m, 1 H (CHO)
Ve	3 408	1 290	1 721	4·45	6·75	7·06—7·85	0·94 d, 6 H (CH_3) 1·72—2·23 m, 1 H (CH) 3·94 d, 2 H (CH_2O)

[a] Compound *Va* in KBr, *Vb*— *Ve* in $CHCl_3$; [b] in $CDCl_3$.

for 10—15 min. After cooling to 0—5°C, the products *IVa—IVj* were filtered and crystallized from an appropriate solvent.

B) Sodium hydride (144 mg, 6 mmol) was added at 0°C to a solution of the urea *IIIf—IIIj* (5 mmol) in N,N-dimethylformamide (30 ml) during 10 min. The mixture was stirred until all the hydride dissolved and then set aside overnight. After pouring into ice-cold water, the solid was filtered and crystallized from an appropriate solvent.

The solvents used for crystallization, yields and physicochemical properties are given in Table III, for spectral data see Table IV.

Alkyl 2-(Bromomethylphenyl)carbamates *Va— Ve*

2-Bromomethylphenyl isocyanate (*II*, 1·06 g, 5 mmol) was dissolved in the corresponding alcohol (1—2 ml). After addition of ether (5 ml) and standing overnight in a refrigerator, the crystalline product was filtered and dried. Yields and physicochemical characteristics are given in Table V, for spectral data see Table VI.

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